Supporting Information

"Synthesis and Sulfur Electrophilicity of the *Nuphar* Thiaspirane Pharmacophore"

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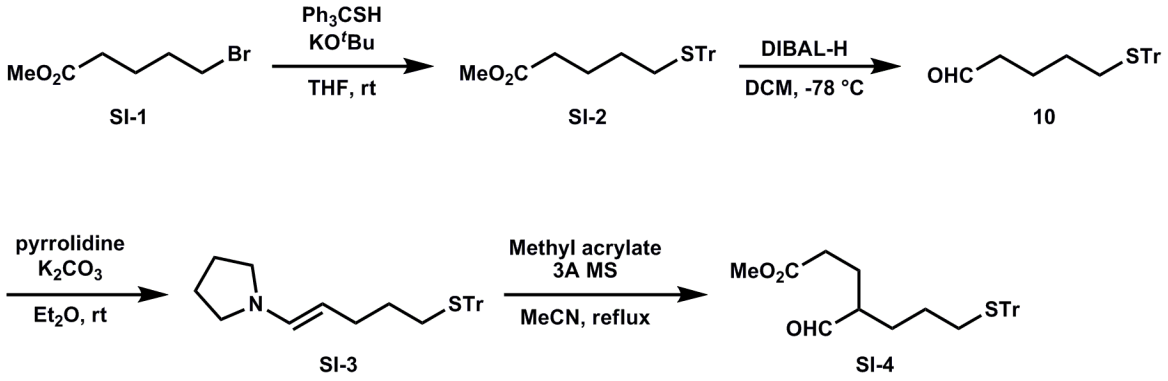
1. Materials and methods

All reactions were carried out under an argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Anhydrous dichloromethane was distilled from calcium hydride (5% w/v) under positive pressure of nitrogen. Anhydrous pentane was distilled from calcium hydride (10% w/v) under positive pressure of nitrogen. Anhydrous HMPA was distilled from calcium hydride (10% w/v) under vacuum. Anhydrous tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl under positive pressure of nitrogen. Diethyl ether, benzene, toluene, dimethylsulfoxide (DMSO), methanol (MeOH), acetonitrile (ACN), N-dimethylformamide (DMF), and triethylamine (Et_3N) were obtained by passing these previously degassed solvents through activated alumina columns. Sodium tetrasulfide (90% technical grade) was purchased from Alfa Aesar. All other reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates from EMD Chemicals (TLC Silica gel 60 F254, 250 μm thickness) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, iodine vapor, or basic aqueous potassium permangante ($KMnO_4$), and heat as developing agents. Preparatory thin layer chromatography (PTLC) was performed using the aforementioned silica gel plates and Analtech Woelm Basic Alumina TLC plates (catalog# 34021 or 34011). Acetone, benzene, hexanes, toluene, *tert*-butanol were distilled to remove traces of plasticizer and grease prior to use in PTLC. Flash column chromatography was performed over silica gel 60 (particle size 0.04-0.063 mm) from EMD Chemicals. NMR spectra were recorded on Bruker DRX-600, DRX-500 or DPX-400 and calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ @ 7.26 ppm ^1H NMR, 77.16 ppm ^{13}C NMR). When taking an NMR of a basic amine, $CDCl_3$ was passed through a short plug of basic alumina (Brockmann activity I, particlesize 0.050-0.200 mm) obtained from Acros Organics. The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, br = broad. GC/MS analysis was performed on Agilent 7820A/5975 GC/MSD system with helium as a carrier gas. Chiral GC analysis was performed on Agilent 7890A GC system with helium as a carrier gas. LC/MS analysis was performed on Agilent 1100 series HPLC/MSD A61946D system with ACN and 0.01% TFA in H_2O as eluents.

2. Experimental Procedures and Characterizations



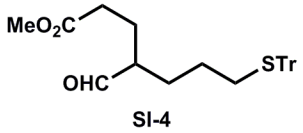
SI-4:[1] To a solution of triphenylmethane thiol (13.96 g, 49.5 mmol, 0.99 eq.) in THF (100 mL), potassium *tert*-butoxide (1.7 M, 33.8 mL, 1.15 eq.) was added and the reaction was stirred for 10 minutes. methyl-5-bromopentanoate **SI-1** (10.05 g, 50 mmol, 1.0 eq.) was then added and the reaction was stirred for 4 hours. The reaction was concentrated *in vacuo* and the residue was diluted with ether. The solution was washed with water and then brine. The organic layer was dried with magnesium sulfate, filtered, and concentrated in vacuo to give the crude trityl sulfide ester **SI-2**.

The trityl sulfide ester **SI-2** (18.55 g, 47.5 mmol, 1 eq.) was dissolved in DCM (200 mL), cooled to -78ºC and treated with DIBAL-H (1.0 M in DCM, 71.3 mL, 1.5 eq.) and stirred for 1 hour at -78ºC. The reaction was monitored by TLC for consumption of the starting material. Upon full consumption, the reaction was quenched with excess methanol. The mixture was warmed to room temperature and excess saturated aqueous Rochelle's salt and stirred for several hours. The organic layer was separated and the aqueous layer was extracted with DCM several times. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the crude aldehyde**10.**

To a solution of the crude aldehyde **10** (17.12 g, 47.5 mmol, 1 eq.) in anhydrous ether (50 mL) under a balloon of argon, anhydrous potassium carbonate (19.7 g, 3 eq.) was added and the suspension was stirred for 2 hours. Pyrrolidine (6.76 g, 95 mmol, 2 eq.) was then added drop wise over 2 minutes. The mixture was then stirred overnight at room temperature. The suspension was then filtered over sand under a stream of nitrogen. The filtrate was concentrated *in vacuo* and the crude enamine residue **SI-3** was used directly in the next step.

The crude enamine **SI-3** (19.65 g, 47.5 mmol, 1 eq.) was dissolved in anhydrous acetonitrile (60 mL) with 3Å mol sieves and cooled to 5ºC. Methyl acrylate (6.89 g, 76 mmol, 1.6

eq.) was added at 5ºC and then the mixture was allowed to room temperature and stirred for 2 hours. Then reaction was then refluxed for 2 hours. The reaction was then cooled to room temperature and treated with acetic acid (10 mL) and water (40 mL) and refluxed for another 2 hours. The reaction was then cooled to room temperature and treated with aqueous HCl (1.0M, 200 mL) and extracted with ethyl acetate three times. The organic layer was washed with brine and was then dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue could then be purified via column chromatography (slow column, 5%->10% ethyl acetate in hexanes) to afford aldehyde **SI-4** in 40% yield from starting ester **SI-1**. The residue could also be used directly in the next reaction as a solution in toluene without significant loss of material.



SI-4

Physical state: slightly yellow oil

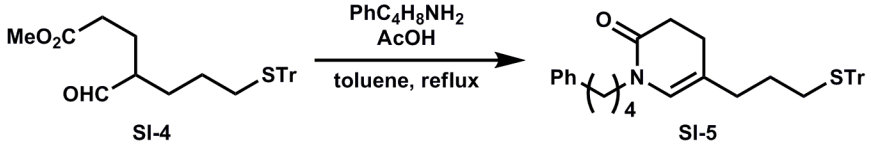
***Rf*=** 0.2 (10% ethyl acetate in hexanes) – stains light green in anisaldehyde

^{1}H NMR ($CDCl_3$, 400 MHz):

δ 9.51 (d, J = 2.3 Hz, 1H), 7.47 – 7.40 (m, 6H), 7.35 – 7.27 (m, 6H), 7.26 – 7.19 (m, 3H), 3.68 (s, 3H), 2.39 – 2.13 (m, 5H), 1.97 – 1.82 (m, 1H), 1.77 – 1.54 (m, 2H), 1.47 – 1.32 (m, 3H)

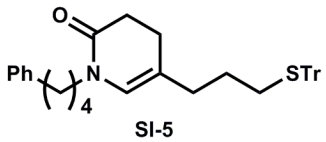
^{13}C NMR ($CDCl_3$, 100 MHz):

δ 203.76, 173.29, 144.84, 129.57, 127.87,126.63, 66.64, 51.68, 50.58, 31.73, 31.25, 27.87, 25.96, 23.40



SI-4 **SI-5**

SI-5: To **SI-4** (4.47 g, 10 mmol, 1 eq.) in toluene (22 mL), 4-phenyl-butylamine (2.98 g, 20 mmol, 2 eq.) and acetic acid (0.601 g, 10 mmol, 1 eq.) are added and the reaction was heated to reflux for 4 hours. The mixture was diluted with aqueous HCl and extracted with ethyl acetate. The organic layer was then washed with water, brine, dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography (10%->20% ethyl acetate in hexanes) to afford enamide **SI-5** in 55% yield.



SI-5

Physical state: colorless oil

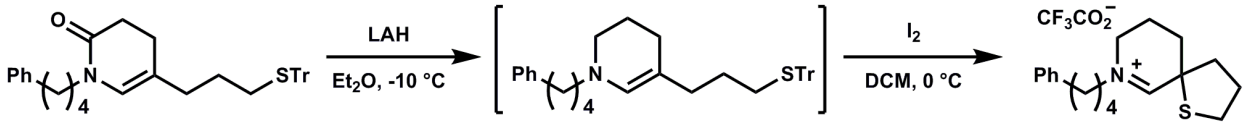
LRMS(APCI) (*m/z*): calculated for $C_{37}H_{40}NOS$ $[M+H]^+$: 546.3 found 546.8

^{1}H NMR ($CDCl_3$, 400 MHz):

δ 7.49 – 7.15 (m, 20 H), 5.67 (s, 1H), 3.44 (t, J = 6.9 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 2.41 (t, J = 8.0Hz, 2H), 2.16 (t, J = 7.2 Hz, 2H), 2.13 – 2.04 (m, 2H), 2.00 (t, J = 7.2 Hz, 2H), 1.70 – 1.40 (m, 6H)

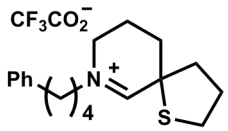
^{13}C NMR ($CDCl_3$, 100 MHz):

δ 168.56, 144.91, 142.16, 129.58, 128.42, 128.34, 127.86, 126.63, 125.80, 124.77, 118.49, 66.58, 45.71, 35.54, 32.87, 31.31, 31.28, 28.45, 28.09, 26.65, 23.79



SI-5 11 13

13: To **SI-5** (38.0mg, 0.0696 mmol, 1 eq.) in anhydrous ether (1.39 mL) under a balloon of argon at -10ºC (care must be taken to run reaction below -5ºC or else trityl group may be cleaved), LAH (4.0 M, 52 μL, 3 eq.) was added slowly and the reaction was stirred for 30 minutes. The reaction was worked up in the usual Feiser manner (this reaction has been run on scales up to 3g of SI-5 without significant deviation in procedure or yield). The flocculent white powder was filtered over sand under a stream of nitrogen and washed with ether several times. Care was taken to minimize exposure of the enamine to air. The filtrate was concentrated *in vacuo* and the residue was taken up in a large amount of DCM (0.001 M in substrate). To a solution of iodine (0.001 M in DCM, 1 eq.) it was added dropwise over the course of 30 minutes at 0ºC. After addition, the mixture was stirred for 30 minutes at 0 ºC, then 1 h at room temperature. The mixture was concentrated *in vacuo* to provide a residue that was taken up in DCM, and was treated with a small amount of trifluoroacetic acid (this reaction has been run on scales up to 1.3g of 11 without significant deviation in procedure or yield). The mixture was concentrated *in vacuo* to provide a 58% ^{1}H NMR yield of **13** (1,3,5-trimethoxybenzene was used as internal standard). The residue was then taken up in acetonitrile and was washed with hexanes (to remove trityl byproducts). The acetonitrile layer was then concentrated and the residue was treated with a small amount of trifluoroacetic acid and purified via preparative HPLC.



13

Physical state: brown oil

LRMS(APCI) (*m/z*): calculated for $C_{18}H_{26}NS$ $[M]^+$: 288.2; found 288.4

λmax1 (acidic MeOH) = ~230 nm; **λmax2 (acidic MeOH) =** ~290 nm

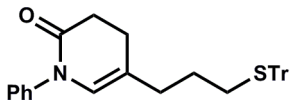
λmax1 (basic MeOH) = ~230 nm

^{1}H NMR (CD_3OD, 400 MHz):

δ 8.62 (s, 1H), 7.33 – 7.15 (m, 5H), 3.94 – 3.76 (m, 2H), 3.76 – 3.57 (m, 2H), 3.13 (t, J = 6.0 Hz, 2H), 2.71 (t, J = 7.4 Hz, 2H), 2.41 – 2.23 (m, 3H), 2.23 – 2.06 (m, 4H), 1.93 –1.77 (m, 3H), 1.77 –1.65 (m, 2H)

^{13}C NMR (CD_3OD, 100 MHz):

δ 173.36, 141.33, 128.09, 128.06, 125.70, 60.61, 56.45, 49.28, 40.11, 34.60, 34.35, 30.04, 29.89, 27.57, 26.20, 20.15



SI-6

SI-6: The title compound was prepared from aldehyde **SI-4** using the same procedure as enamide **SI-5** (above) with aniline. The residue was then purified by column chromatography (20% ethyl acetate in hexanes) to afford enamide **SI-6** in 61% yield (1.15g).

Physical state: colorless solid

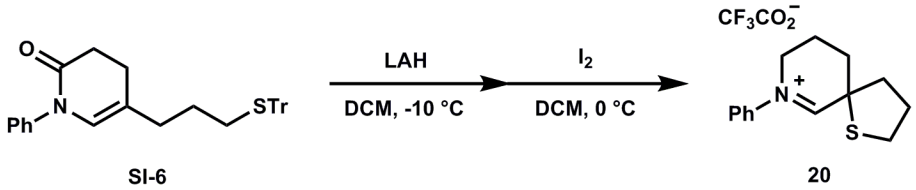
LRMS (APCI) (*m/z*): calculated for $C_{33}H_{32}NOS$ $[M+H]^+$: 490.2; found 489.9

^{1}H NMR ($CDCl_3$, 500 MHz):

δ 7.54 –7.26 (m, 15H), 6.03 (s, 1H), 2.67 (t, J = 8.0 Hz, 2H), 2.30 (t, J = 8.0 Hz, 2H), 2.26 (t, J = 7.4 Hz, 2H), 2.17 – 2.10 (m, 2H), 1.62 (quint, J = 7.3 Hz, 2H).

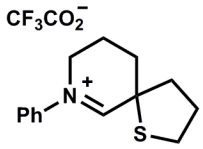
^{13}C NMR ($CDCl_3$, 126 MHz):

δ 168.94, 145.31, 141.18, 129.99, 129.38, 128.27, 127.19, 127.04, 126.54, 126.39, 119.57, 67.04, 33.29, 32.46, 31.68, 26.96, 24.28.



SI-6 20

20: To enamide **SI-6** (53.3 mg, 0.1088 mmol, 1 eq.) in anhydrous DCM (218 μL) under a balloon of argon at -10 ºC, LAH (4.0 M, 82 μL, 3 eq.) was added slowly and the reaction was stirred for 30 minutes. The reaction was worked up in the usual Feiser manner. The flocculent white powder was filtered over sand under a stream of nitrogen and washed with ether several times. Care was taken to minimize exposure of the enamine to air. The filtrate was concentrated *in vacuo* and the residue was taken up in a large amount of DCM (0.001 M in substrate). To a solution of iodine (0.001 M in DCM, 1 eq.) it was added dropwise over the course of 30 minutes at 0 ºC. After addition, the mixture was stirred for 30 minutes at 0 ºC, then 1 h at room temperature. The mixture was concentrated *in vacuo* to provide a residue that was taken up in DCM, and was treated with a small amount of trifluoroacetic acid. The mixture was concentrated *in vacuo* to provide a 61% ^{1}H NMR yield of **20** (1,1,2,2-tetrachloroethane was used as internal standard). The residue was purified via preparative HPLC.



20

Physical state: brown oil

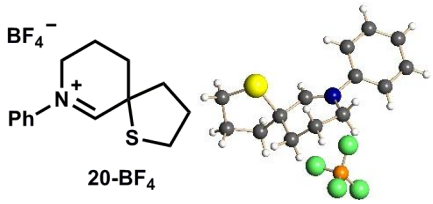
LRMS(APCI) (*m/z*): calculated for $C_{14}H_{18}NS$ $[M]^+$: 232.1; found 231.9

^{1}H NMR ($CDCl_3$, 600 MHz):

δ 8.60 (s, 1H), 7.59 – 7.53 (m, 3H), 7.53 – 7.47 (m, 2H), 4.48 (m, 1H), 3.85 (dd, J = 15.0, 5.4 Hz, 1H), 3.19 (dt, J = 10.6, 6.2 Hz, 1H), 3.12 (dt, J = 10.5, 6.5 Hz, 1H), 2.61 (ddd, J = 13.6, 6.6, 5.4 Hz, 1H), 2.52 (td, J = 13.7, 3.3 Hz, 1H), 2.41 – 2.20 (m, 5H), 2.07 – 1.96 (m, 1H).

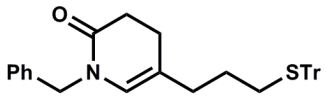
^{13}C NMR ($CDCl_3$, 151 MHz):

δ 170.83, 160.00 (q, J = 37.8 Hz), 142.41, 130.83, 129.88, 121.65, 115.33 (q, J = 289.9 Hz), 57.61, 52.37, 39.99, 35.01, 29.83, 29.11, 20.71.



20-BF4

20-BF4: To a solution of **20** (28.6 mg) in DCM (3 mL), 1 equivalents of aqueous 50% HBF_4 was added. The mixture was stirred for ten minutes and then concentrated under a stream of nitrogen and then high-vacuum. The residue was decanted with Et_2O, and recrystallized with DCM, Et_2O and hexane in refrigerator. See page SI-47 for x-ray data.



SI-7c

SI-7c: The title compound was prepared from aldehyde **SI-4** using the same procedure as enamide **SI-5** (above) with benzylamine. The residue was then purified by column chromatography (10%->20% ethyl acetate in hexanes) to afford enamide **SI-7c** in72% yield.

Physical state: yellow solid

LRMS(APCI) (*m/z*): calculated for $C_{34}H_{34}NOS$ $[M+H]^+$: 504.2 found 504.7

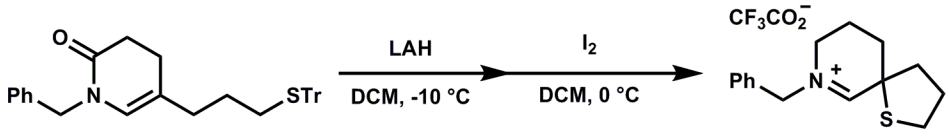
***Rf*=** 0.2 (20% ethyl acetate in hexanes)

^{1}H NMR ($CDCl_3$, 400 MHz):

δ 7.49 – 7.18 (m, 20H), 5.70 (s, 1H), 4.65 (s, 2H), 2.50 (t, J = 8.0 Hz, 2H), 2.20 – 2.08 (m, 4H), 1.96 (t, J = 7.4 Hz, 2H), 1.46 (quint, J = 7.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz):

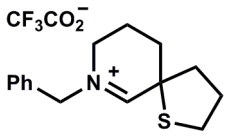
δ 168.79, 144.90, 137.30, 129.58, 128.62, 127.85, 127.54, 127.39, 126.61, 124.41, 118.99, 66.61, 48.84, 32.90, 31.29, 31.22, 26.65, 23.85



SI-7c 21c

21c: To enamide **SI-7c** (55.2 mg, 0.1096 mmol, 1 eq.) in anhydrous DCM (219 μL) under a balloon of argon at -10 ºC (care must be taken to run reaction below -5ºC or else trityl group may be cleaved), LAH (4.0 M, 82 μL, 3 eq.) was added slowly and the reaction was stirred for 30 minutes. The reaction was worked up in the usual Feiser manner (this reaction has been run on scales up to 1.8g of SI-7c without significant deviation in procedure or yield). The flocculent white powder

was filtered over sand under a stream of nitrogen and washed with ether several times. Care was taken to minimize exposure of the enamine to air. The filtrate was concentrated *in vacuo* and the residue was taken up in a large amount of DCM (0.001 M in substrate). To a solution of iodine (0.001 M in DCM, 1 eq.), it was added dropwise over the course of 30 minutes at 0 °C. After addition, the mixture was stirred for 30 minutes at 0 °C, then 5 min at room temperature. The mixture was treated with a small amount of trifluoroacetic acid (this reaction has been run on scales up to 0.6 g without significant deviation in procedure or yield). The mixture was concentrated *in vacuo* to provide a 57% ^{1}H NMR yield of **21c** (1,1,2,2-tetrachloroethane was used as internal standard). The residue was purified via preparative HPLC.



21c

Physical state: brown oil

LRMS(APCI) (*m*/*z*): calculated for $C_{15}H_{20}NS$ $[M]^+$: 246.1; found 246.4

λmax1 (acidic MeOH) = ~230 nm; **λmax2 (acidic MeOH) =** ~290 nm

λmax1 (basic MeOH) = ~230 nm

^{1}H NMR (CD_3OD, 400 MHz):

δ 8.89 (s, 1H), 7.56 – 7.41 (m, 5H), 5.14 (d, J = 14.0 Hz, 1H), 5.01 – 4.91 (m, 1H), 3.67 – 3.53 (m, 2H), 3.24 – 3.09 (m, 2H), 2.45 – 2.28 (m, 3H), 2.28 – 2.06 (m, 4H), 1.81 – 1.64 (m, 1H).

^{13}C NMR (CD_3OD, 100 MHz):

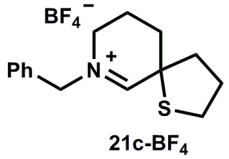
δ 173.32, 130.95, 129.58, 129.20, 128.76, 63.87, 56.79, 48.82, 40.04, 34.41, 29.90, 29.88, 20.23

^{1}H NMR ($CDCl_3$, 400 MHz):

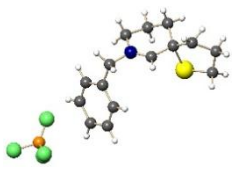
δ 8.85 (s, 1H), 7.57 – 7.42 (m, 3H), 7.35 – 7.21 (m, 2H), 6.13 (brs), 5.22 (d, J = 14.2 Hz, 1H),4.78 (d, J = 14.2 Hz, 1H), 3.76 – 3.65 (m, 2H), 3.43 (dd, J = 15.4, 2H), 2.39 – 2.09 (m, 7H), 1.76 –1.65 (m, 1H)

^{13}C NMR ($CDCl_3$, 151 MHz):

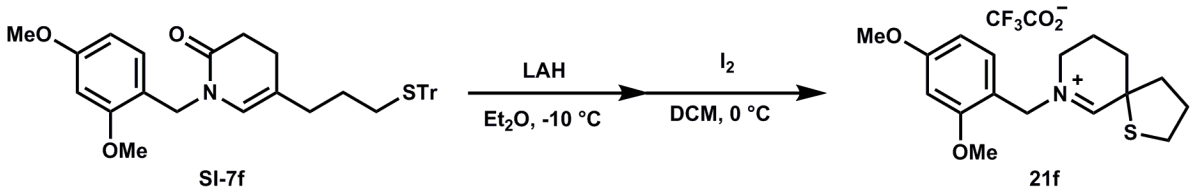
δ 172.52, 130.58, 130.13, 129.82, 129.01, 64.74, 57.13, 48.63, 40.60, 35.26, 30.36, 30.25, 20.89.



21c-BF_4

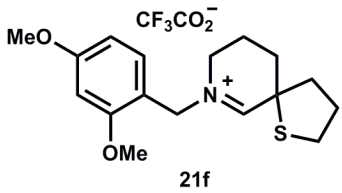


21c-BF_4: To a solution of **21c** (10mg) in DCM (1 mL), 1 equivalents of aqueous 50% HBF_4 was added. The mixture was stirred for ten minutes and then concentrated under a stream of nitrogen and then high-vacuum. The residue was decanted with Et_2O, and recrystallized with DCM, Et_2O and hexane in refrigerator. See page S56 for x-ray data.



SI-7f 21f

21f: The title compound was prepared from enamide **SI-7f** (48.1 mg, 0.0852 mmol, 1 eq.) using the same procedure as butyl phenyl iminium **13** to provide a 40% ^1H NMR yield of **21f** (1,1,2,2-tetrachloroethane was used as internal standard). The residue was purified via preparative HPLC.



21f

Physical state: brown oil

LRMS(APCI) (*m/z*): calculated for $C_{17}H_{24}NO_2S$ $[M]^+$: 306.2; found 305.9

^1H NMR ($CDCl_3$, 600 MHz):

δ 8.39 (s, 1H), 7.24 (d, J = 8.3 Hz, 1H), 6.55 – 6.48 (m, 2H), 5.04 (d, J = 13.9 Hz, 1H), 4.68 (d, J = 13.9 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.70 – 3.61 (m, 1H), 3.56 – 3.49 (m, 1H), 3.15 – 3.03 (m, 2H), 2.37 – 2.29 (m, 2H), 2.29 – 2.20 (m, 1H), 2.19 – 2.05 (m, 4H), 1.76 – 1.65 (m, 1H).

^{13}C NMR ($CDCl_3$, 151 MHz):

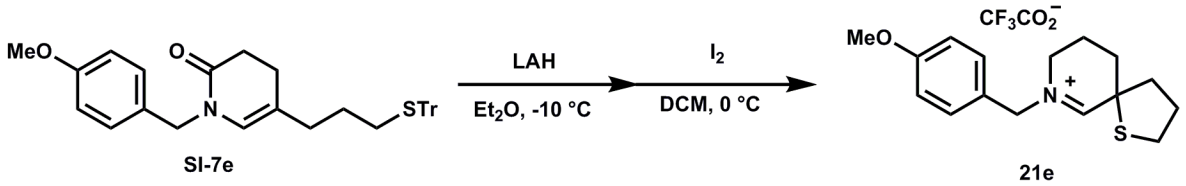
δ 171.35, 162.41, 160.11 (q, J = 36.2 Hz), 158.90, 132.50, 115.53 (q, J = 288.41 Hz), 109.54, 104.53, 98.49, 60.61, 55.95, 55.05, 54.99, 47.97, 40.26, 34.50, 30.22, 29.87, 19.88.

^1H NMR (CD_3OD, 400 MHz):

δ 8.63 (s, 1H), 7.32 (d, J = 8.3 Hz, 1H), 6.67 – 6.57 (m, 2H), 5.03 (d, J = 13.7 Hz, 1H), 4.84 (d, J = 13.7 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.65 – 3.49 (m, 2H), 3.19 – 3.08 (m, 2H), 2.44 – 2.03 (m, 7H), 1.79 – 1.63 (m, 1H).

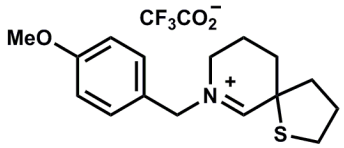
^{13}C NMR (CD_3OD, 101 MHz):

δ 172.34, 163.08, 159.63, 132.53, 110.42, 104.97, 98.38, 60.55, 56.26, 54.75, 54.63, 48.36, 40.30, 34.29, 30.47, 30.00, 20.02.



SI-7e 21e

21e: The title compound was prepared from enamide **SI-7e** (45.9 mg, 0.0860 mmol, 1 eq.) using the same procedure as butyl phenyl iminium **13** to provide a 42% ^{1}H NMR yield of **21e** (1,1,2,2-tetrachloroethane was used as internal standard). The residue was purified via preparative HPLC.



21e

Physical state: brown oil

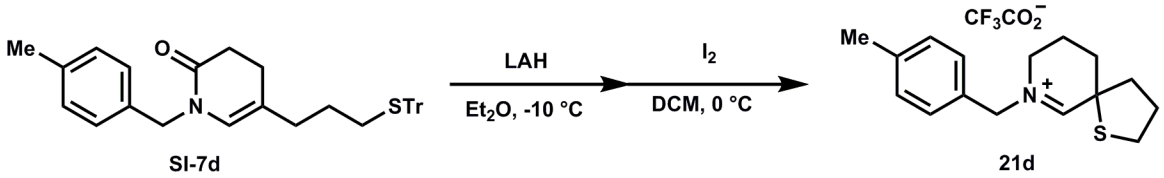
LRMS(APCI) (*m/z*): calculated for $C_{16}H_{22}NOS$ $[M]^+$: 276.1; found 275.9

^{1}H NMR (CD_3OD, 400 MHz):

δ 8.79 (s, 1H), 7.44 – 7.35 (m, 2H), 7.07 – 6.99 (m, 2H), 5.04 (d, J = 13.9 Hz, 1H), 4.87 (d, J = 13.9 Hz, 1H), 3.84 (s, 3H), 3.65 – 3.51 (m, 2H), 3.22 – 3.08 (m, 2H), 2.44 – 2.26 (m, 3H), 2.26 – 2.06 (m, 4H), 1.79 – 1.63 (m, 1H).

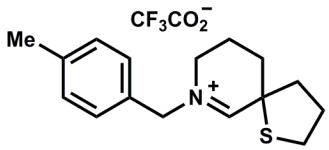
^{13}C NMR (CD_3OD, 101 MHz):

δ 171.66, 161.02, 130.47, 122.46, 114.50, 63.55, 56.70, 54.49, 48.60, 40.06, 34.37, 30.01, 29.91, 20.20.



SI-7d 21d

21d: The title compound was prepared from enamide **SI-7d** (38.4 mg, 0.0742 mmol, 1 eq.) using the same procedure as butyl phenyl iminium **13** to provide a 44% ^{1}H NMR yield of **21d** (1,1,2,2-tetrachloroethane was used as internal standard). The residue was purified via preparative HPLC.



21d

Physical state: brown oil

LRMS(APCI) (*m/z*): calculated for $C_{16}H_{22}NS$ $[M]^+$: 260.2; found 259.9

^{1}H NMR ($CDCl_3$, 600 MHz):

δ 8.78 (s, 1H), 7.28 – 7.27 (m, 4H), 5.16 (d, J = 14.2 Hz, 1H), 4.73 (d, J = 14.2 Hz, 1H), 3.75 – 3.65 (m, 1H), 3.46 (dd, J = 15.6, 5.5 Hz, 1H), 3.17 (dt, J = 10.4, 6.1 Hz, 1H), 3.08 (dt, J = 10.4, 6.1 Hz, 1H), 2.52 (dt, J = 13.4, 5.9 Hz, 1H), 2.40 (s, 3H), 2.39 – 2.22 (m, 3H), 2.19 – 2.10 (m, 3H), 1.77 – 1.66 (m, 1H).

^{13}C NMR ($CDCl_3$, 151 MHz):

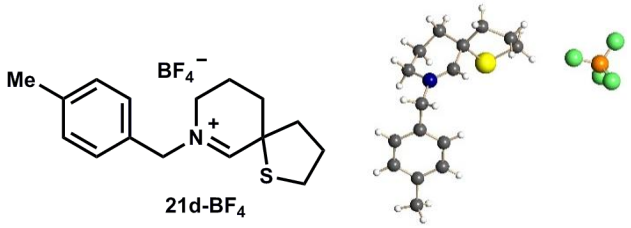
δ 171.53, 139.79, 129.89, 128.44, 126.66, 64.06, 56.45, 47.93, 39.99, 34.64, 29.76, 29.70, 20.79, 20.26.

^{1}H NMR (CD_3OD, 600 MHz):

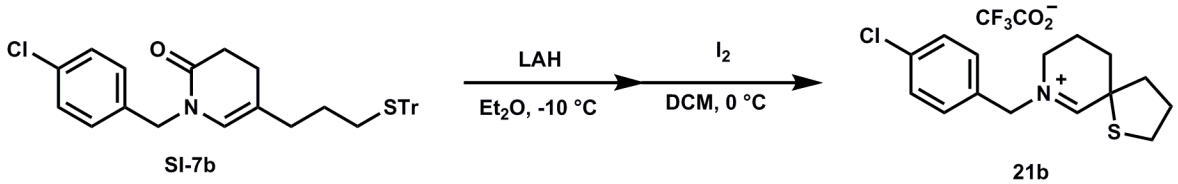
δ 8.85 (s, 1H), 7.38 – 7.29 (m, 4H), 5.08 (d, J = 13.9 Hz, 1H), 4.90 (d, J = 13.9 Hz, 1H), 3.60 (m, 2H), 3.16 (m, 2H), 2.39 (s, 3H), 2.44 – 2.28 (m, 3H), 2.26 – 2.08 (m, 4H), 1.77 – 1.66 (m, 1H).

^{13}C NMR (CD_3OD, 151 MHz):

δ 171.54, 159.52 (q, J = 37.8 Hz), 139.50, 129.32, 128.35, 127.38, 115.63 (q, J = 289.9 Hz), 63.25, 56.28, 48.24, 39.59, 33.93, 29.49, 29.45, 19.76, 19.39.

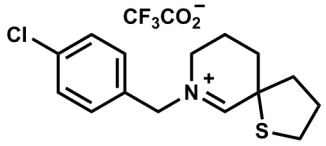


21d-BF_4: To a solution of **21d** (12mg) in DCM (1 mL), 1 equivalents of aqueous 50% HBF_4 was added. The mixture was stirred for ten minutes and then concentrated under a stream of nitrogen and then high-vacuum. The residue was decanted with Et_2O, and recrystallized with DCM, Et_2O and hexane in refrigerator. See page S66 for x-ray data.



21b: The title compound was prepared from enamide **SI-7b** (46.6 mg, 0.0866 mmol, 1 eq.) using the same procedure as butyl phenyl iminium **13** to provide a 46% ^{1}H NMR yield of **21b** (1,1,2,2-tetrachloroethane was used as internal standard). The residue was purified via

preparative HPLC.



21b

Physical state: brown oil

LRMS(APCI) (*m/z*): calculated for $C_{15}H_{19}ClNS$ $[M]^+$: 280.1; found 279.9

^{1}H NMR ($CDCl_3$, 600 MHz):

δ 8.80 (d, J = 2.0 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.34 – 7.30 (m, 2H), 5.19 (d, J = 14.4 Hz, 1H), 4.78 (d, J = 14.4 Hz, 1H), 3.76 – 3.66 (m, 1H), 3.44 (dd, J = 15.6, 5.5 Hz, 1H), 3.19 (dt, J = 10.4, 6.1 Hz, 1H), 3.10 (dt, J = 10.4, 6.1 Hz, 1H), 2.49 (dt, J = 13.4, 5.8 Hz, 1H), 2.40 – 2.29 (m, 2H), 2.29 – 2.21 (m, 1H), 2.21 – 2.12m,3H), 1.79 – 1.67 (m, 1H).

^{13}C NMR ($CDCl_3$, 151 MHz):

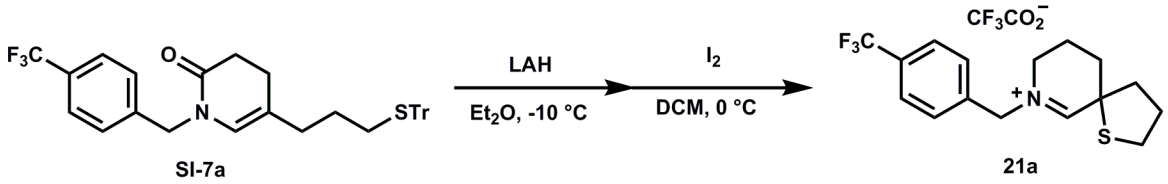
δ 171.56, 160.21 (q, J = 37.8 Hz), 135.81, 130.06, 129.40, 128.22, 115.50 (q, J = 289.9 Hz), 63.18, 56.44, 48.31, 39.80, 34.60, 29.68, 29.47, 20.11.

^{1}H NMR (CD_3OD, 500 MHz):

δ 8.94 (s, 1H), 7.60 – 7.50 (m, 4H), 5.21 – 5.10 (m, 1H), 5.02 (d, J = 14.1 Hz, 1H), 3.69 – 3.62 (m, 2H), 3.32 – 3.16 (m, 2H), 2.49 – 2.34 (m, 3H), 2.37 – 2.14 (m, 4H), 1.87 – 1.72 (m, 1H).

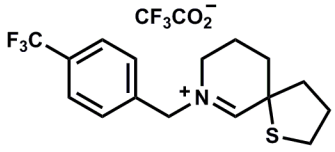
^{13}C NMR (CD_3OD, 101 MHz):

δ 172.51, 159.26 (q, J = 38.4 Hz), 135.67, 130.47, 129.66, 129.29, 115.55 (q, J = 288.9 Hz), 63.00, 56.86, 48.88, 39.99, 34.42, 29.87, 29.76, 20.22.



SI-7a **21a**

21a: The title compound was prepared from enamide **SI-7a** (57.1 mg, 0.0999 mmol, 1 eq.) using the same procedure as butyl phenyl iminium **13** to provide a 46% ^{1}H NMR yield of **21a** (1,1,2,2-tetrachloroethane was used as internal standard). The residue was purified via preparative HPLC.



21a

Physical state: slightly yellow solid

LRMS(APCI) (*m/z*): calculated for $C_{16}H_{19}F_3NS$ $[M]^+$: 314.1; found 313.9

^{1}H NMR ($CDCl_3$, 600 MHz):

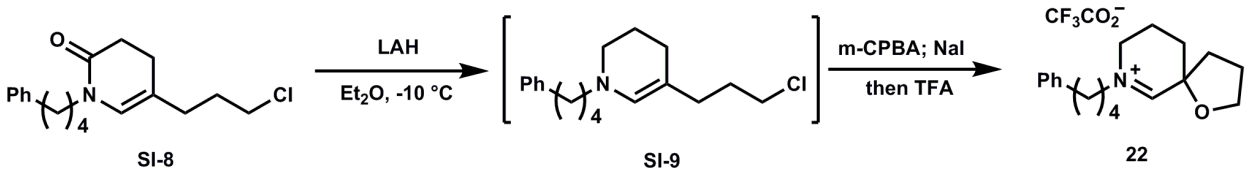
δ 8.84 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 5.27 (d, J = 14.4 Hz, 1H), 4.90 (d, J = 14.4 Hz, 1H), 3.74 – 3.65 (m, 1H), 3.49 – 3.42 (m, 1H), 3.19 (dt, J = 10.4, 6.1 Hz, 1H), 3.10 (dt, J = 10.4, 6.1 Hz, 1H), 2.49 – 2.42 (m, 1H), 2.39 – 2.27 (m, 2H), 2.26 – 2.12 (m, 4H), 1.81 – 1.67 (m, 1H).

^{1}H NMR (CD_3OD, 400 MHz):

δ 8.98 (s, 1H), 7.81 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 5.23 (d, J = 14.2 Hz, 1H), 5.14 – 4.94 (m, 1H), 3.70 – 3.53 (m, 2H), 3.23 – 3.11 (m, 2H), 2.46 – 2.29 (m, 3H), 2.29 – 2.09 (m, 4H), 1.86 – 1.67 (m, 1H).

^{13}C NMR (CD_3OD, 151 MHz):

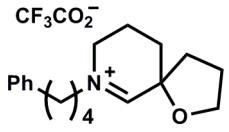
δ 172.65, 159.41 (q, J = 37.8 Hz), 134.94, 131.02 (q, J = 33.2 Hz), 128.94, 125.58 (q, J = 3.0 Hz), 123.37 (q, J = 271.8 Hz), 115.48 (q, J = 289.9 Hz), 62.52, 56.49, 48.68, 39.53, 34.03, 29.41, 29.19, 19.80.



22: The chloro enamide **SI-8** was prepared in a similar manner as **SI-5** using the corresponding chloro aldehyde. **SI-8** appeared to be unstable so it was taken forward without characterization. The chloro enamide **SI-8** was reduced with LAH in the usual manner to afford the chloro enamine **SI-9**.

The chloro enamine **SI-9** (290 mg, 0.994 mmol, 1 eq.) in acetonitrile (60 mL) was treated with *m*-CPBA (73%, 276 mg, 1.17 mmol, 1.18 eq.) at room temperature. The reaction was stirred at room temperature for 15 minutes, then, sodium iodide (1.21 g, 8.12 mmol, 8.17 eq.) was added and the reaction was heated to 100ºC for 12 hours. The reaction was concentrated *in vacuo* and the residue was diluted with DCM. The solution was washed with aqueous sodium carbonate, aqueous sodium thiosulfate, then water, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was treated with a small amount of TFA and taken up in a small amount of acetonitrile and water and purified via preparative HPLC to yield 0.13 g (37%) of the title compound. The compound existed as a ~9:1 mixture of hemiaminal:iminium in deuteromethanol and ~5:1 mixture of hemiaminal:iminium in

deuterobenzene.



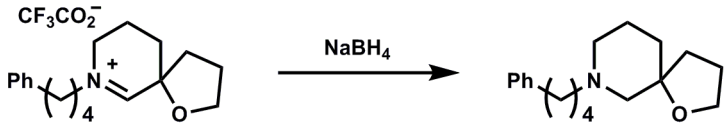
22

Physical state: slightly yellow oil

LRMS(APCI) (*m/z*): calculated for $C_{18}H_{26}NO$ $[M]^+$: 272.2 found 272.4

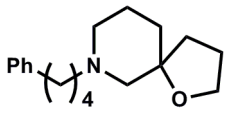
λmax1 (acidic MeOH) = ~230 nm

λmax1 (basic MeOH) = ~230 nm



22 SI-10

SI-10: To a solution of **22** (10 mg, 0.026 mmol, 1 eq.) in methanol (1 mL), sodium borohydride (3 mg, 0.079 mmol, 3 eq.) was added and the reaction was stirred for 5 minutes. The crude reaction mixture was concentrated under a stream of nitrogen and the residue was taken up in DCM. The suspension was filtered through a plug of basic alumina and concentrated *in vacuo* to afford **SI-10** in 85% yield.



SI-10

Physical state: slightly yellow oil

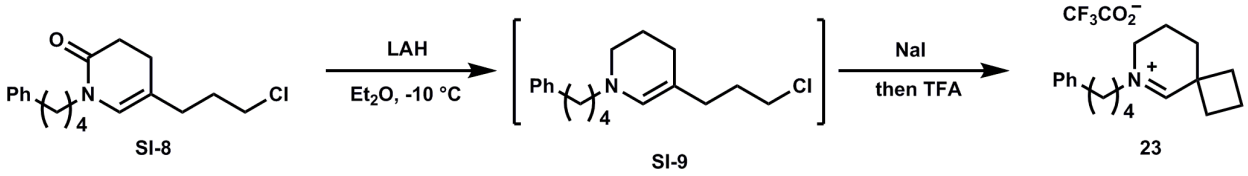
LRMS(APCI) (*m/z*): calculated for $C_{18}H_{28}NO$ $[M+H]^+$: 274.2 found 274.4

^{1}H NMR (C_6D_6, 600 MHz):

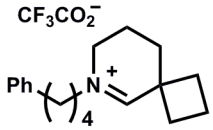
δ 7.21 – 7.04 (m, 5H), 3.70 (t, *J* = 6.6 Hz, 2H), 2.54 – 2.43 (m, 3H), 2.26 – 2.15 (m, 2H), 2.11 – 2.04 (d, J = 10.6 Hz, 1H), 1.96 – 1.80 (m, 2H), 1.66 – 1.19 (m, 12H)

^{13}C NMR (C_6D_6, 151 MHz):

δ127.92, 127.80, 127.51, 125.21, 80.25, 66.26, 62.45, 57.65, 53.04, 35.88, 35.32, 34.49, 28.74, 25.97, 25.32, 23.19



23: The chloro enamine **SI-9** (360 mg, 1.22 mmol, 1 eq.) in acetonitrile (60 mL) was treated with sodium iodide (1.1 g, 7.4 mmol, 6 eq.) at room temperature. The reaction was then heated to 100ºC for 12 hours. The reaction was concentrated *in vacuo* and the residue was diluted with DCM. The solution was washed with aqueous sodium carbonate, aqueous sodium thiosulfate, then water, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was treated with a small amount of TFA and taken up in a small amount of acetonitrile and water and purified via preparative HPLC to yield 0.19 g (46%) of **23**.



Physical state: slightly yellow oil

LRMS(APCI) (*m/z*): calculated for $C_{18}H_{26}N$ $[M]^+$: 256.2 found 256.4

λmax1 (acidic MeOH) = ~230 nm

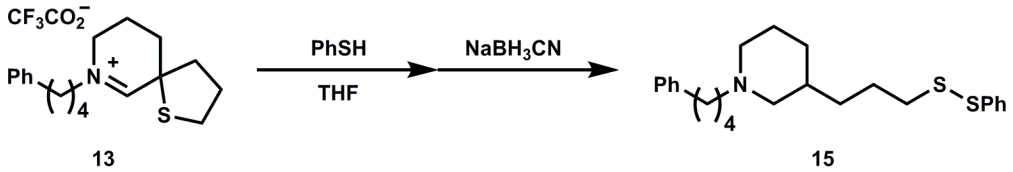
λmax1 (basic MeOH) = ~230 nm

^{1}H NMR (CD_3OD, 600 MHz):

δ 8.83 (s, 1H), 7.32 – 7.27 (m, 2H), 7.25 – 7.21 (m, 2H), 7.21 – 7.17 (m, 1H), 3.87 (t, J = 7.6 Hz, 2H), 3.67 (td, J = 5.8, 1.6 Hz, 2H), 2.72 (t, J = 7.5 Hz, 2H), 2.55 – 2.47 (m, 2H), 2.28 – 2.07 (m, 4H), 2.01 – 1.95 (m, 2H), 1.95 – 1.83 (m, 4H), 1.73 – 1.66 (m, 2H).

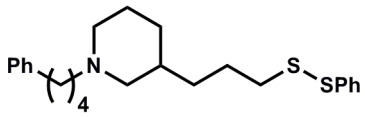
^{13}C NMR (CD_3OD, 151 MHz):

δ 180.72, 160.56 (q, J = 34.3 Hz), 140.92, 127.67, 127.61, 125.27, 114.2 (q, J = 283.9 Hz), 60.83, 49.79, 41.58, 34.13, 29.89, 27.13, 27.10, 25.80, 17.53, 15.00.



15: To a solution of **13** (16.8 mg, 0.042 mmol, 1 eq.) in THF (0.3 mL) at room temperature under argon, thiophenol (461 mg, 4.18 mmol, 100 eq.) was added and the reaction was stirred for 24

hours. At this point sodium cyanoborohydride (13.15 mg, 0.209 mmol, 5 eq.) was added and the reaction was stirred for 10 minutes (nearly full conversion to disulfide by LC/MS). The reaction was quenched with aqueous HCl to help prevent over reduction (if left for >1 hour, significant amounts of amine thiol is produced). The reaction was concentrated under a stream of nitrogen and residual thiophenol was removed *in vacuo*. The residue was diluted with DCM and washed with aqueous sodium carbonate. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was subjected to column chromatography (gradient, DCM -> 5% MeOH in DCM) to afford the title compound in 80% yield.



15

Physical state: slightly yellow oil

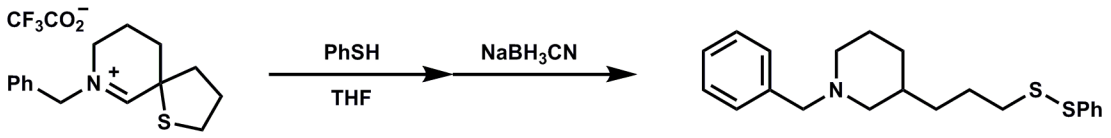
LRMS(APCI) (*m/z*): calculated for $C_{24}H_{34}NS_2$ $[M+H]^+$: 400.2; found 400.6

^{1}H NMR (CD_3OD, 600 MHz):

δ 7.57 – 7.53 (m, 2H), 7.38 – 7.32 (m, 2H), 7.30 – 7.23 (m, 3H), 7.23 – 7.19 (m, 2H), 7.19 – 7.15 (m, 1H), 3.13 (d, J = 11.8 Hz, 1H), 3.06 – 3.00 (m, 1H), 2.77 (t, J = 7.1 Hz, 1H), 2.72 – 2.60 (m, 4H), 2.26 (t, J = 11.5 Hz, 1H),1.94 (t, J = 11.5 Hz, 1H), 1.81 – 1.53 (m, 7H), 1.39 – 1.24 (m, 5H), 1.00 – 0.89 (m, 2H)

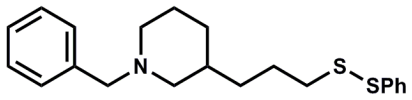
^{13}C NMR (CD_3OD, 151 MHz):

δ 141.33, 137.03, 128.27, 127.59, 127.54, 126.79, 126.13, 125.06, 58.13, 57.43, 52.76, 38.02, 34.57, 34.08, 31.84, 28.88, 28.30, 24.89, 24.02, 23.14.



21c **SI-10c**

SI-10c: The title compound was prepared from iminium **21c** using the same procedure as **15** (above). The residue was subjected to preparative TLC (Hexane:EtOAc = 4:1) to afford the title compound in 56% yield.



SI-10c

Physical state: slightly yellow oil

LRMS(APCI) (*m/z*): calculated for $C_{21}H_{28}NS_2$ $[M+H]^+$: 358.2; found 358.2

^{1}H NMR (CD_3OD, 600 MHz):

δ 7.56 – 7.51 (m, 2H), 7.41 – 7.31 (m, 7H), 7.27 – 7.21 (m, 1H), 3.72 – 3.64 (m, 2H), 2.97 (d, J = 11.8 Hz, 1H), 2.95 – 2.90 (m, 1H), 2.74 (t, J = 7.1 Hz, 2H), 2.17 – 2.10 (m, 1H), 1.82 (t, J = 11.2 Hz, 1H), 1.78 – 1.50 (m, 6H), 1.36 – 1.23 (m, 2H), 0.95 – 0.84 (m, 1H).

^{13}C NMR (CD_3OD, 151 MHz):

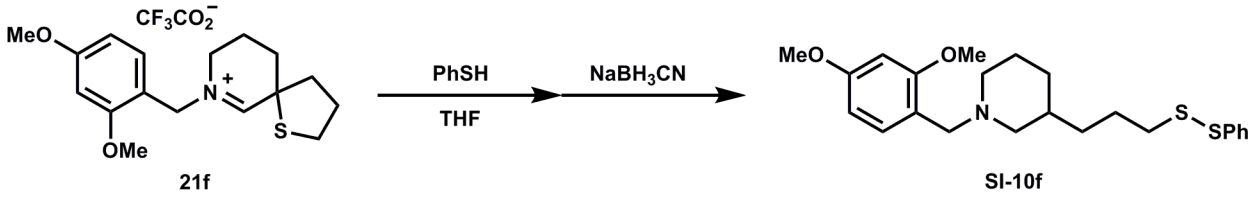
δ 137.05, 134.65, 129.36, 128.23, 127.64, 127.19, 126.79, 126.10, 62.06, 58.48, 52.84, 38.08, 34.32, 32.08, 29.37,25.00, 23.53

^{1}H NMR ($CDCl_3$, 600 MHz):

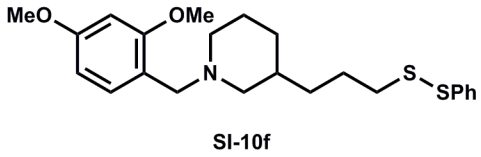
δ 7.58 – 7.52 (m, 2H), 7.38 – 7.26 (m, 7H), 7.25 – 7.21 (m, 1H), 3.62 – 3.44 (m, 2H), 2.91 – 2.77 (m, 2H), 2.72 (t, J = 7.2 Hz, 2H), 1.97 – 1.86 (m, 1H), 1.77 – 1.50 (m, 7H), 1.40 – 1.19 (m, 2H), 0.88 – 0.79 (m, 1H).

^{13}C NMR ($CDCl_3$, 151 MHz):

δ 137.12, 129.07, 128.48, 127.80, 127.07, 126.83, 126.27, 62.64, 59.21, 53.24, 38.61, 35.07, 34.84, 33.28, 32.67, 31.48, 30.02, 29.26, 29.22, 29.01, 28.91, 25.47, 24.35, 22.25, 22.23, 13.69.



SI-10f: The title compound was prepared from iminium **21f** using the same procedure as **15** (above). The residue was subjected to preparative TLC (Hexane:EtOAc = 4:1) to afford the title compound in36% yield.



SI-10f

Physical state: slightly yellow oil

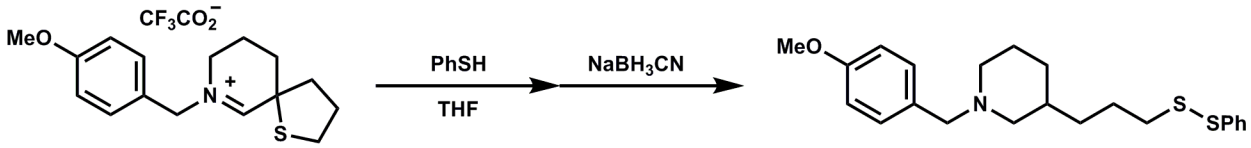
LRMS(APCI) (*m/z*): calculated for $C_{23}H_{32}NO_2S_2$ $[M+H]^+$: 418.2; found 417.9

^{1}H NMR ($CDCl_3$, 600 MHz):

δ 7.57 – 7.52 (m, 2H), 7.33 (t, J = 9.0 Hz, 2H), 7.26 – 7.20 (m, 2H), 6.51 – 6.45 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 2.86 (t, J = 11.3 Hz, 2H), 2.73 (t, J = 7.2 Hz, 2H), 1.94 (t, J = 11.4 Hz, 1H), 1.75 – 1.50 (m, 7H), 1.33 – 1.19 (m, 2H), 0.86 – 0.77 (m, 1H).

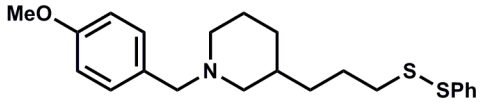
^{13}C NMR ($CDCl_3$, 151 MHz):

δ 159.40, 158.39, 137.15, 131.01, 128.47, 127.06, 126.25, 103.46, 97.95, 59.43, 55.52, 54.97, 53.29, 38.69, 35.12, 32.88, 30.31, 29.25, 25.61, 24.78, 13.67.



21e SI-10e

SI-10e: The title compound was prepared from iminium **21e** using the same procedure as **15** (above). The residue was subjected to preparative TLC (Hexane:EtOAc = 4:1) to afford the title compound in 49% yield.



SI-10e

Physical state: slightly yellow oil

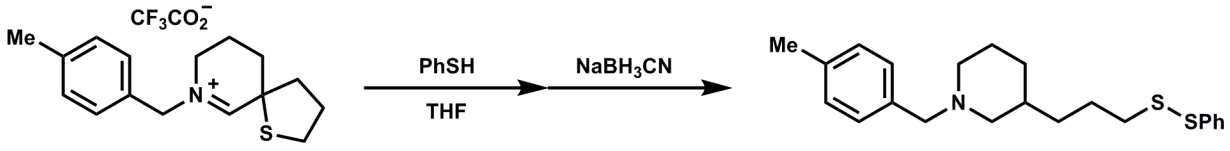
LRMS(APCI) (*m/z*): calculated for $C_{22}H_{30}NOS_2$ $[M+H]^+$: 388.2; found 387.9

^{1}H NMR ($CDCl_3$, 600 MHz):

δ 7.57 – 7.52 (m, 2H), 7.37 – 7.30 (m, 2H), 7.26 – 7.21 (m, 3H), 6.90 – 6.84 (m, 2H), 3.83 (s, 3H), 3.49 – 3.36 (m, 2H), 2.79 (t, J = 12 Hz, 2H), 2.73 (t, J = 9 Hz, 2H), 1.87 (t, J = 12 Hz, 1H), 1.75 – 1.48 (m, 7H), 1.33 – 1.18 (m, 2H), 0.88 – 0.78 (m, 1H).

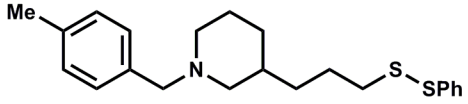
^{13}C NMR ($CDCl_3$, 151 MHz):

δ 158.15, 137.16, 129.93, 128.52, 127.06, 126.25, 113.08, 62.45, 59.58, 54.78, 53.48, 38.70, 35.22, 32.80, 30.35, 29.25, 25.61, 24.78.



21d SI-10d

SI-10d: The title compound was prepared from iminium **21d** using the same procedure as **15** (above). The residue was subjected to preparative TLC (Hexane:EtOAc = 4:1) to afford the title compound in 75% yield.



SI-10d

Physical state: slightly yellow oil

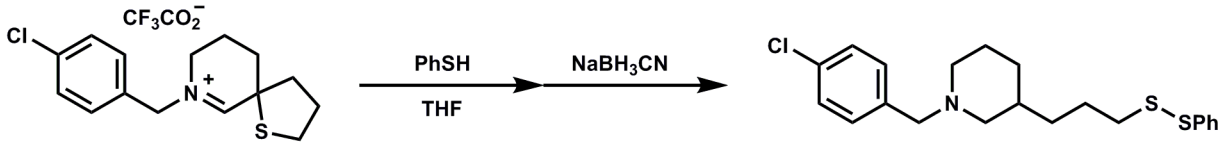
LRMS(APCI) (*m/z*): calculated for $C_{22}H_{30}NS_2$ $[M+H]^+$: 372.2; found 371.9

^{1}H NMR ($CDCl_3$, 600 MHz):

δ 7.57 – 7.53 (m, 2H), 7.33 (t, J = 7.8 Hz, 2H), 7.26 – 7.22 (m, 1H), 7.21 (d, J = 7.7 Hz, 2H), 7.14 (d, J = 7.7 Hz, 2H), 3.49 (d, J = 13.0 Hz, 1H), 3.44 (d, J = 13.0 Hz, 1H), 2.85 – 2.76 (m, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.36 (s, 3H), 1.92 – 1.85 (m, 1H), 1.78 – 1.49 (m, 7H), 1.40 – 1.19 (m, 2H), 0.97-0.79 (m, 1H).

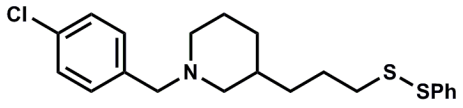
^{13}C NMR ($CDCl_3$, 151 MHz):

δ 137.17, 136.03, 129.70, 128.77, 128.47, 128.37, 127.06, 126.25, 62.79, 59.64, 53.52, 38.71, 35.21, 32.79, 30.31, 29.18, 25.61, 20.65.



21b **SI-10b**

SI-10b: The title compound was prepared from iminium **21b** using the same procedure as **15** (above). The residue was subjected to preparative TLC (Hexane:EtOAc = 4:1) to afford the title compound in 41% yield.



SI-10b

Physical state: slightly yellow oil

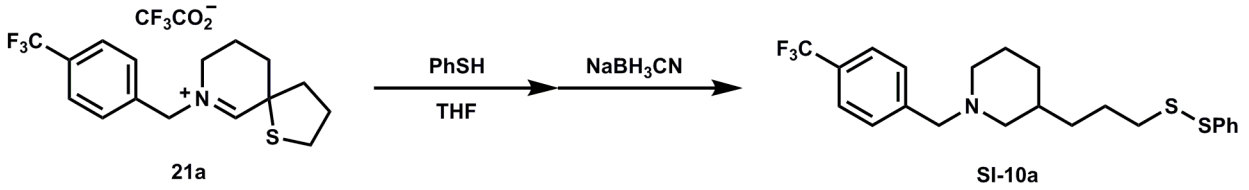
LRMS (APCI) (*m/z*): calculated for $C_{21}H_{27}ClNS_2$ $[M+H]^+$: 392.1; found 391.8

^{1}H NMR ($CDCl_3$,600 MHz):

δ 7.54 (d, J = 8.4 Hz, 2H), 7.36 – 7.20 (m, 7H), 3.45 (q, J = 13.3 Hz, 2H), 2.76 (t, J = 12.8 Hz, 2H), 2.72 (t, J = 7.2 Hz, 2H), 1.94 – 1.87 (m, 1H), 1.76 – 1.49 (m, 7H), 1.35 – 1.19 (m, 2H), 0.94 – 0.81 (m, 1H).

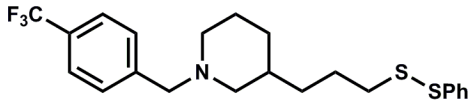
13C NMR ($CDCl_3$, 151 MHz):

δ 137.13, 136.38, 132.18, 129.96, 128.47, 127.84, 127.05, 126.26, 62.26, 59.62, 53.62, 38.66, 35.21, 32.69, 30.22, 29.25, 25.59.



21a SI-10a

SI-10a: The title compound was prepared from iminium **21a** using the same procedure as **15** (above). The residue was subjected to column chromatography (DCM:EtOAc = 2:1) to afford the title compound in 21% yield.



SI-10a

Physical state: slightly yellow oil

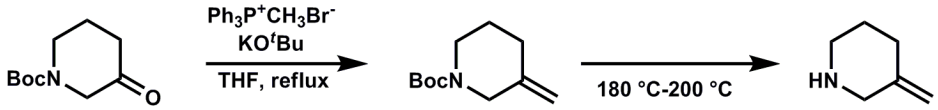
LRMS(APCI) (*m/z*): calculated for $C_{22}H_{27}F_3NS_2$ $[M+H]^+$: 426.2; found 425.8

^{1}H NMR ($CDCl_3$, 600 MHz):

δ 7.59 (d, J = 8.0 Hz, 2H), 7.57 – 7.53 (m, 2H), 7.46 (d, J = 7.9 Hz, 2H), 7.36 – 7.30 (m, 2H), 7.26 – 7.21 (m, 1H), 3.56 (d, J = 13.6 Hz, 1H), 3.51 (d, J = 13.6 Hz, 1H), 2.80 – 2.69 (m, 4H), 1.93 (t, J = 9 Hz, 1H), 1.77 – 1.50 (m, 7H), 1.33 – 1.21 (m, 2H), 0.87 (qd, J = 12.3, 4.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 151 MHz):

δ 137.13, 128.71, 128.47, 127.02, 126.26, 124.65 (q, J = 3.5 Hz), 123.83 (q, J = 271.8 Hz), 62.49, 59.79, 53.72, 38.65, 35.25, 32.66, 30.16, 25.59, 24.72.



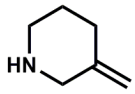
SI-11 SI-12 SI-13

SI-13: To a suspension of methyltriphenylphosphonium bromide (26.8 g, 75 mmol, 1.5 eq.) in THF (150 mL), potassium *tert*-butoxide (1.7 M in THF, 70 mL, 1.4 eq.) was added and the mixture was heated to reflux for 1 hour. Then, *N*-Boc-3-keto-piperidine (9.96 g, 50 mmol, 1 eq.) as a solution in THF (100 mL) was added and the reaction was refluxed for 2 hours. The reaction was then cooled and concentrated *in vacuo* and the residue was diluted with ether and hexanes. The organic layer was washed with water and brine, then dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified via column chromatography (5% ethyl acetate in hexanes) to afford the *N*-Boc-3-methylene-piperidine **SI-12** contaminated with a small amount of triphenylphosphine oxide in 71% yield.

Neat *N*-Boc-3-methylene-piperidine **SI-12** (4.3 g, 22 mmol) in a flask with a distillation short

path attached was heated to 180ºC - 200ºC (oil bath temperature) to induce Boc deprotection. The free amine was distilled out of the reaction at the same temperature during the process of deprotection to afford the free amine **SI-13** in 50% yield.

Note, the amine may absorb carbon dioxide from the reaction or from the atmosphere, therefore it should be kept under nitrogen or argon.



SI-13

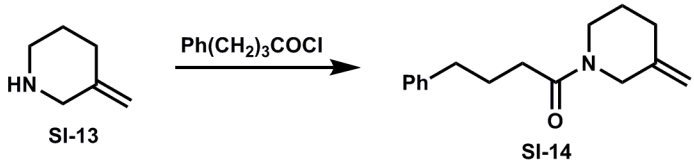
Physical state: colorless oil

^{1}H NMR ($CDCl_3$, 400 MHz):

δ 4.69 (d, J = 11.3 Hz, 2H), 3.32 (s, 2H), 2.90 (br s, 2H), 2.29 (t, J = 6.3 Hz, 1H), 1.96 (m,1H), 1.71 – 1.60(m, 2H).

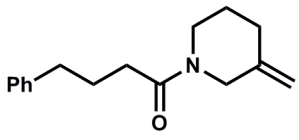
^{13}C NMR ($CDCl_3$, 101 MHz):

δ 107.66, 53.40, 46.59, 33.35, 29.71.



SI-13 SI-14

SI-14: To a solution of amine **SI-13** (2.5 g, 25.7 mmol, 1 eq.) and trimethylamine (4.17 g, 41.2 mmol, 1.6 eq.) in dichloromethane (50 mL) at 0ºC, 4-phenyl-butyrylchloride (7.31 g, 40 mmol, 1.55 eq.) was added slowly over 5 minutes. The reaction was stirred for an additional 30 minutes at room temperature and then diluted with water. The layers were separated and then washed with 1M HCl, water, and brine. The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to give amide essentially pure **SI-14** in 99% yield.



SI-14

Physical state: slightly yellow solid

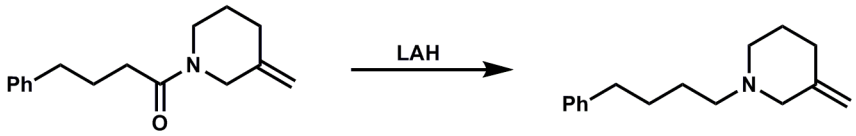
LRMS(APCI) (*m/z*): calculated for C16H21NO [M]+: 244.4 found 224.4

^{1}H NMR ($CDCl_3$, 400 MHz):

1:1 Mixture of rotamers δ 7.32 – 7.08 (m, 10H), 4.93 (s,1H), 4.73 (s, 1H), 4.62 (s, 1H), 4.57 (s, 1H), 4.19 (s, 1H), 3.60 (m, 2H), 3.42 (s, 2H), 2.80 (m, 2H), 2.68 (t, J = 7.0 Hz, 4H), 2.21 – 1.91 (m, 12H), 1.43 – 1.31 (m, 2H), 1.25 – 1.13 (m,2H).

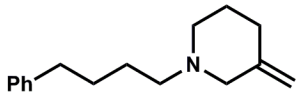
^{13}C NMR ($CDCl_3$, 101 MHz):

Mixture of rotamers δ 176.26, 171.13, 142.81, 141.77, 141.48, 128.51, 128.34, 125.88, 110.78, 110.12, 52.63, 48.34, 45.76, 42.22, 35.36, 32.70, 27.24, 26.76, 26.42.



SI-14 SI-15

SI-15: To a solution of amide **SI-14** (4.5 g, 18.5 mmol, 1 eq.) in ether (20 mL) at 0ºC, LAH (4.0 M in ether, 9.25 mL, 2 eq.) was added slowly over 5 minutes. The reaction was stirred for an additional 60 minutes at 0ºC. The reaction was then worked up in the following manner: 1.4 mL of water, 1.4 mL of 15% NaOH, then 4.2 mL water. A fine precipitate was formed, filtered over cotton, and washed with ether several times. The filtrate was concentrated *in vacuo* to yield essentially pure amine **SI-15** in 82% yield.



SI-15

Physical state: colorless oil

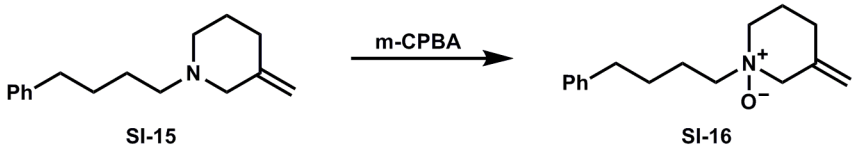
LRMS(APCI) (*m/z*): calculated for C16H23N [M]+: 230.3 found 230.3

^{1}H NMR ($CDCl_3$, 400 MHz):

δ 7.34 – 7.15 (m, 5H), 4.77 (d, J = 9.4 Hz, 2H), 2.92 (s, 2H), 2.65 (t, J = 7.5 Hz, 2H), 2.53 – 2.45 (m, 2H), 2.43 – 2.35 (m, 2H), 2.17 (t, J = 6.4 Hz, 1H), 1.79– 1.51 (m, 6H)

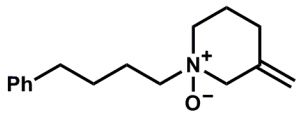
^{13}C NMR ($CDCl_3$, 101 MHz):

δ 144.67, 142.51, 128.40, 128.25, 125.66, 109.10, 60.63, 58.65, 53.77, 35.86, 32.85, 29.53, 26.71, 26.40



SI-15 SI-16

SI-16: To a solution of amine **SI-15** (5.15 g, 22.45 mmol, 1 eq.) in DCM (100 mL) at 0ºC, *m*-CPBA (73%, 5.3 g, 22.45 mmol, 1 eq.) was added slowly over 10 minutes at 0ºC. The mixture was concentrated *in vacuo* and the residue was loaded onto basic alumina (grade I) and eluted (1%->5% MeOH in DCM). The residue was then re-chromatographed on silica (1%->10% MeOH in DCM) to afford *N*-oxide **SI-16** in 50%yield.



SI-16

Physical state: white solid

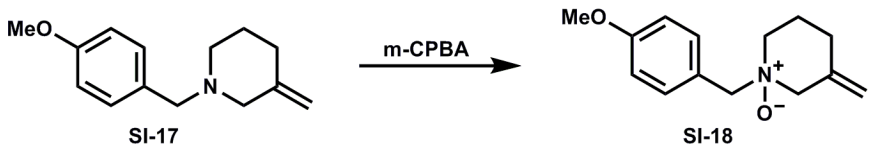
LRMS(APCI) (*m/z*): calculated for C16H23NO [M]+: 246.3 found 246.3

^{1}H NMR ($CDCl_3$, 600 MHz):

δ 7.32 – 7.15 (m, 5H), 5.09 (s, 1H), 5.01 (s, 1H), 3.79 (d, J = 12.8 Hz, 1H), 3.71 (d, J = 12.8 Hz, 1H), 3.45 – 3.39 (m, 1H), 3.33 – 3.26 (m, 1H), 3.23 – 3.10 (m, 2H), 2.72 – 2.66 (m, 2H), 2.34 – 2.28 (m, 2H), 2.18 – 2.08 (m, 1H), 2.05 – 1.85 (m, 2H), 1.73 – 1.61 (m, 2H)

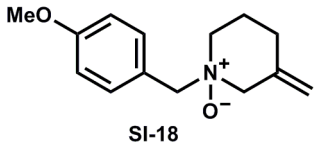
^{13}C NMR ($CDCl_3$, 151 MHz):

δ 141.18, 138.09, 127.94, 127.90, 125.50, 115.50, 72.25, 65.23, 65.18, 35.16, 30.12, 28.18, 21.88, 21.23



SI-17 SI-18

SI-18: The title compound was prepared from amine **SI-13** using the same procedure as amine oxide **SI-16** (above). The residue was chromatographed on silica (0%-20% MeOH in DCM) to afford *N*-oxide **SI-18** in 44% yield in three step.



SI-18

Physical state: white solid

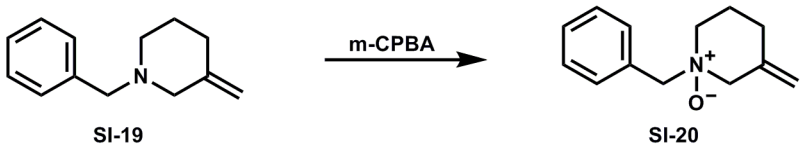
LRMS(APCI) (*m/z*): calculated for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.2 found 233.9

^{1}H NMR ($CDCl_3$, 600 MHz):

δ 7.47 (dd, J = 8.9, 2.7 Hz, 1H), 6.93 – 6.87 (m, 1H), 5.10 (s, 1H), 5.01 (s, 1H), 4.30 (qd, J = 12.8, 2.6 Hz, 1H), 3.83 – 3.79 (m, 3H), 3.76 (d, J = 12.7 Hz, 1H), 3.59 (d, J = 12.7Hz, 1H), 3.43 – 3.39 (m, 1H), 3.29 – 3.17 (m, 2H), 2.37 – 2.29 (m, 1H), 2.29 – 2.21 (m, 1H), 2.21 – 2.12 (m, 1H), 1.78 – 1.70 (m, 1H)

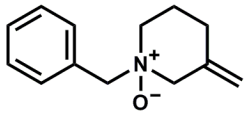
^{13}C NMR ($CDCl_3$, 151 MHz):

δ 160.04, 137.92, 133.30, 121.50, 115.67, 113.41, 71.21, 70.37, 63.61, 54.81, 30.06, 21.38



SI-19 SI-20

SI-20: The title compound was prepared from amine **SI-13** using the same procedure as amine oxide **SI-16** (above). The residue was chromatographed on silica (0%-20% MeOH in DCM) to afford *N*-oxide **SI-20** in 55%yield in three step.



SI-20

Physical state: white solid

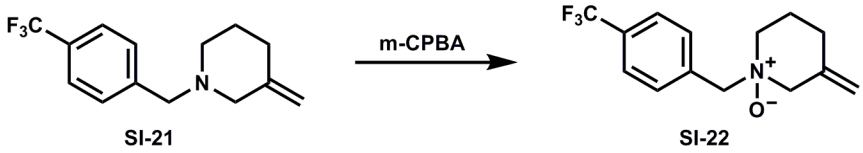
LRMS(APCI) (*m/z*): calculated for C13H18NO $[M+H]^+$: 204.1 found 203.9

^{1}H NMR ($CDCl_3$, 600 MHz):

δ 7.61 – 7.55 (m, 2H), 7.45 – 7.36 (m, 3H), 5.11 (d, J = 5.4 Hz, 1H), 5.01 (d, J = 5.8 Hz, 1H), 4.45 – 4.34 (m, 2H), 3.84 (dd, J = 12.7, 4.2 Hz, 1H), 3.63 (dd, J = 12.8, 6.0 Hz, 1H), 3.45 – 3.40 (m, 1H), 3.38 – 3.30 (m, 1H), 3.29 – 3.20 (m, 1H), 2.39 – 2.31 (m, 1H), 2.31 – 2.16 (m, 2H), 1.82 – 1.72 (m, 1H)

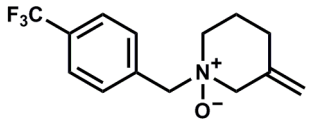
^{13}C NMR ($CDCl_3$, 151 MHz):

δ 138.28, 132.56, 129.86, 129.53, 128.50, 116.23, 72.17, 71.16, 64.38, 30.50, 21.84.



SI-21 SI-22

SI-22: The title compound was prepared from amine **SI-13** using the same procedure as amine oxide **SI-16** (above). The residue was chromatographed on silica (0%-20% MeOH in DCM) to afford *N*-oxide **SI-22** in 12%yield in three step.



SI-22

Physical state: colorless oil

LRMS(APCI) (*m/z*): calculated for C14H17F3NO $[M+H]^+$: 272.1 found 271.9

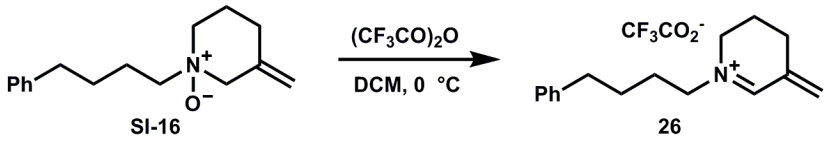
^{1}H NMR ($CDCl_3$, 600 MHz):

δ 7.77 (d, J = 7.9 Hz, 2H), 7.64 (d, J = 7.9 Hz, 2H), 5.14 (s, 1H), 5.02 (s, 1H), 4.38 (qd, J = 12.4, 3.2 Hz, 2H), 3.80 (d, J = 12.7 Hz, 1H), 3.64 (d, J = 12.7, 1H), 3.36 – 3.29 (m, 1H), 3.29 – 3.23 (m, 1H),

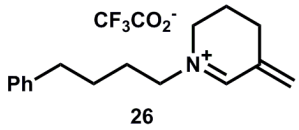
2.40 – 2.26 (m, 2H), 2.26 – 2.17 (m, 1H), 1.84 – 1.75 (m, 1H).

^{13}C NMR ($CDCl_3$, 151 MHz):

δ 137.71, 133.21, 132.52, 131.06 (q, J = 33.2 Hz), 124.76 (q, J = 4.4 Hz), 123.42 (q, J = 271.8 Hz), 116.05, 71.75, 69.37, 65.08, 30.10, 21.67.



26: To a solution of **SI-16** (25 mg, 0.102 mmol, 1 eq.) in dichloromethane (2 mL) at 0ºC, trifluoroacetic anhydride (0.144 mL, 1.02 mmol, 10 eq.) was added dropwise and the solution was stirred at 0ºC for 2 hours. The reaction was monitored by LC/MS, and NMR for disappearance of starting material and formation of iminium ion. Upon completion of the reaction, solution was concentrated under a stream of nitrogen to afford the title compound **26**.



Physical state: slightly yellow oil

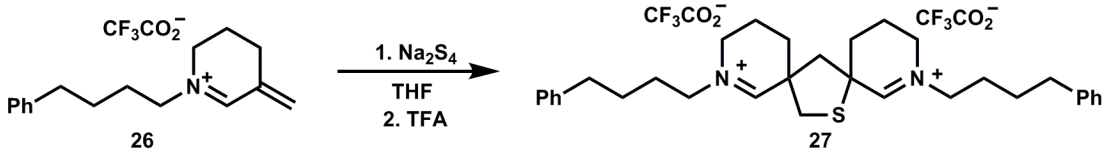
LRMS(APCI) (*m/z*): calculated for C16H22N [M]+: 228.3 found 228.3

^{1}H NMR (CD_3OD, 400 MHz):

δ 8.74 (s, 1H), 7.33 – 7.14 (m, 5H), 6.39 (d, J = 7.0 Hz, 2H), 3.93 (t, J = 7.6 Hz, 2H), 3.80 (t, J = 5.7 Hz, 2H), 2.72 (t, J = 7.5 Hz, 2H), 2.66 – 2.58 (m, 2H), 2.05 (quint, J = 6.0 Hz, 2H), 1.92 – 1.84 (m, 2H), 1.78 – 1.67 (m, 2H)

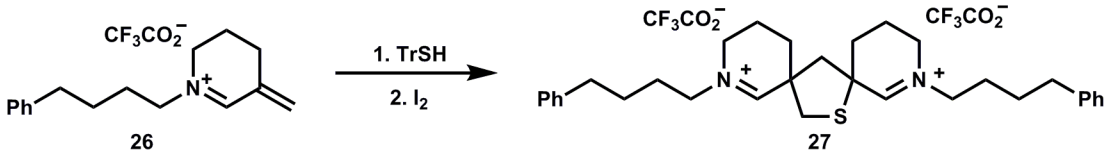
^{13}C NMR (CD_3OD, 151 MHz):

δ 169.71, 160.12 (J = 38.5 Hz), 142.16, 140.54, 137.63, 128.95, 128.89, 126.56, 116.49 (J = 286.9 Hz), 61.64, 54.24, 50.89, 35.49, 28.54, 27.21, 24.25, 20.88

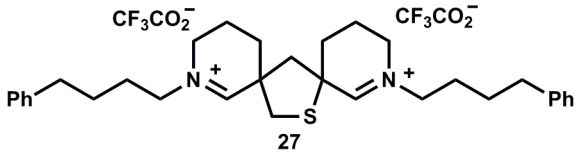


27(One step dimerization): To iminium **26** (0.205 mmol, 1 eq.), sodium tetrasulfide (20.3 mg, 0.121 mmol, 0.51 eq.) was added, followed by non-anhydrous THF (1 mL). The red suspension was stirred for 6 hours and monitored by LC/MS for formation of dimers. When the reaction did not proceed any further, the reaction mixture was concentrated under a stream of nitrogen. The

reaction was diluted with DCM and basified with aqueous sodium carbonate. The mixture was washed with water once and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated and diluted with acetonitrile and a small amount of trifluoroacetic acid was added (at least 2 eq.). The acetonitrile was then extracted with carbon disulfide two times to help remove residual sulfur. The acetonitrile layer was then concentrated under a stream of nitrogen. The mixture was then diluted with a small amount of water and purified by preparative HPLC to afford **27** in 34% yield.



27 (Stepwise dimerization)**:** the iminium **26** was generated as before and triphenylmethanethiol (0.5 eq.) was added. The reaction was stirred and monitored by LC/MS for conversion to the enamine trityl sulfide. After full conversion was seen, the reaction was treated with iodine (0.5 eq.) and monitored for conversion to the dimer. When the reaction was complete, the mixture was concentrated under a stream of nitrogen. The residue was taken up in acetonitrile then washed with hexanes to help remove the trityl byproducts. The acetonitrile layer was then concentrated and the residue was subjected to preparative HPLC.



Physical state: slightly yellow oil

LRMS(APCI) (*m/z*): calculated for $C_{32}H_{45}N_2OS$ [M+OH]+: 505.3 found 505.7

λmax1 (acidic MeOH) = ~230 nm; **λmax2 (acidic MeOH) =** ~290 nm

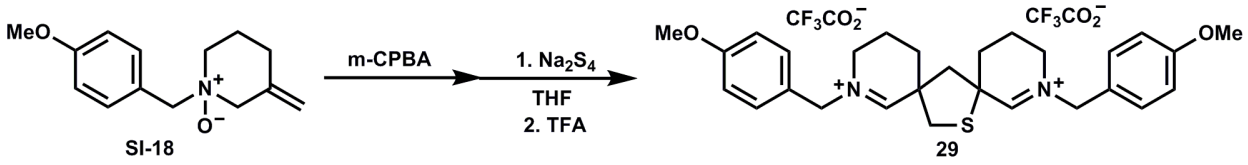
λmax1 (basic MeOH) = ~230 nm

^{1}H NMR (CD_3OD, 600 MHz):

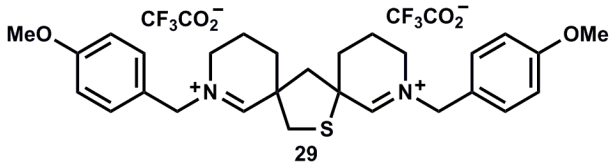
δ 8.80 (s, 1H), 8.68 (s, 1H), 7.30 – 7.13 (m, 10H), 4.04 –3.57 (m, 8H), 3.40 (d, J = 13.0 Hz, 1H), 3.36 –3.26(m, 1H), 2.76 – 2.51 (m, 7H), 2.30 – 1.62 (m, 15H)

^{13}C NMR (CD_3OD, 151 MHz):

δ 177.55, 171.83, 140.83, 140.79, 127.65, 127.64, 127.60, 125.26, 62.02, 60.62, 56.49, 51.90, 50.58, 48.65, 41.07, 34.18, 30.44, 27.20, 27.15, 26.63, 25.72, 25.75, 19.57, 17.98



29: The title compound was prepared from *N*-oxide **SI-18** using the same procedure (above). The residue was subjected to preparative HPLC to afford 28.9 mg (15%) of dimer **29**.



Physical state: slightly yellow oil

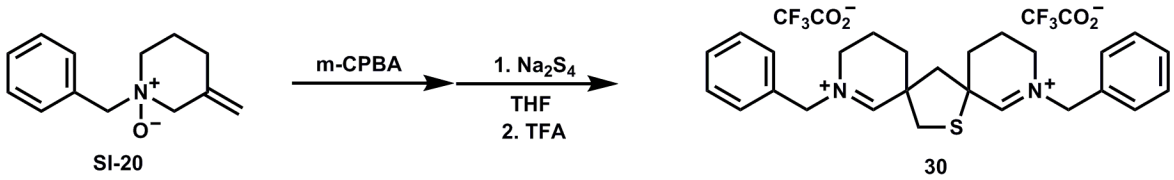
LRMS(APCI) (*m/z*): calculated for $C_{28}H_{37}N_2O_3S$ $[M+OH]^+$: 481.3 found 480.9

^{1}H NMR (CD_3CN, 600 MHz):

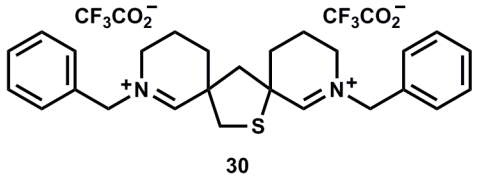
δ 8.20 (s, 1H), 8.15 (s, 1H), 7.41 – 7.37 (m, 4H), 7.08 – 7.04 (m, 4H), 4.90 (d, J = 14.4 Hz, 1H), 4.83 (d, J = 14.4 Hz, 1H), 3.85 (s, 6H), 3.77 – 3.37 (m, 5H), 3.00 – 2.95 (m, 1H), 2.53 (d, J = 14.3 Hz, 1H), 2.31 – 2.13 (m, 4H), 2.10 – 2.01 (m, 2H), 2.01 – 1.90 (m, 2H), 1.89 – 1.83 (m, 1H), 1.78 – 1.68 (m, 1H).

^{13}C NMR (CD_3CN, 151 MHz):

δ 176.15, 170.28, 160.61, 160.52, 131.68, 131.26, 131.02, 121.00, 120.47, 144.32, 113.88, 109.52, 64.62, 63.45, 56.48, 54.72, 54.71, 51.84, 51.06, 49.18, 48.43, 41.38, 30.73, 26.69, 19.53, 17.93



30: The title compound was prepared from *N*-oxide **SI-20** using the same procedure (above). The residue was subjected to preparative HPLC to afford14.9 mg (4%) of dimer **30**.



Physical state: slightly yellow oil

LRMS(APCI) (*m/z*): calculated for $C_{26}H_{33}N_2OS$ $[M+OH]^+$: 421.2 found 421.3

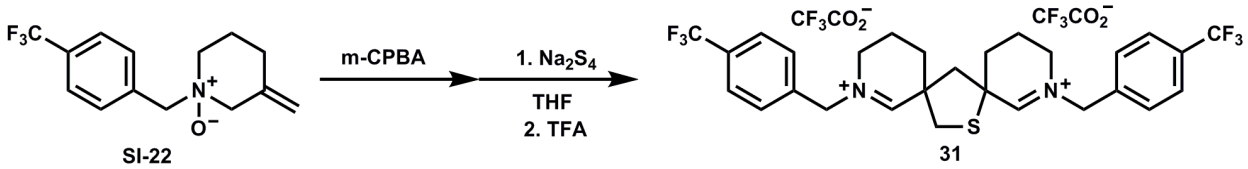
^{1}H NMR (CD_3CN, 600 MHz):

δ 8.84 (s, 1H), 8.75 (s, 1H), 7.56 – 7.44 (m, 10H), 5.13 – 4.98 (m, 1H), 4.93 (d, J = 14.2 Hz, 1H),

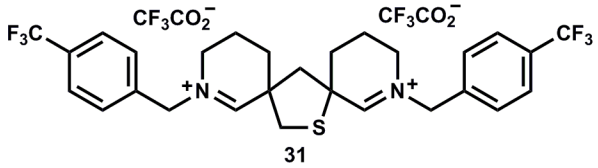
3.76 – 3.44 (m, 4H), 3.02 (d, J = 12.2 Hz, 1H), 2.85 (d, J = 14.3 Hz, 1H), 2.32 – 1.84 (m, 7H), 1.77 – 1.67 (m, 1H)

^{13}C NMR (CD_3CN, 151 MHz):

δ 178.05, 171.89, 129.89, 129.70, 129.61, 129.46, 129.30, 129.26, 128.95, 65.15, 63.84, 56.66, 52.10, 50.76, 48.84, 48.34, 41.39, 30.42, 26.84, 19.72, 18.00



31: The title compound was prepared from *N*-oxide **SI-22** using the same procedure (above). The residue was subjected to preparative HPLC to afford 10.0 mg (27%) of dimer **31**.



Physical state: slightly yellow oil

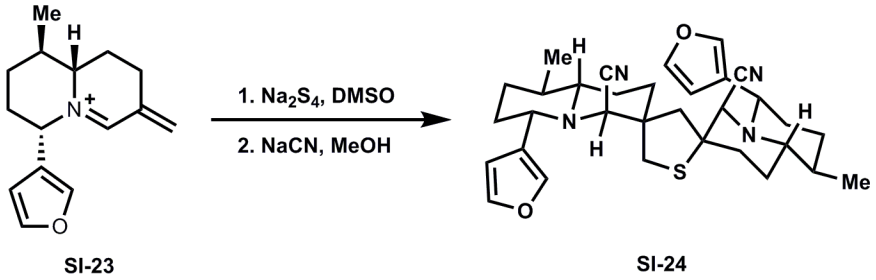
LRMS(APCI) (*m/z*): calculated for $C_{28}H_{31}F_6N_2OS$ $[M+OH]^+$: 557.2 found 556.8

^{1}H NMR (CD_3CN, 600 MHz):

δ 8.83 (s, 1H), 8.75 (s, 1H), 7.84 (d, J = 7.9 Hz, 4H), 7.72 – 7.67 (m, 4H), 5.22 – 5.10 (m, 1H), 5.03 (d, J = 14.4 Hz, 1H), 3.75 – 3.49 (m, 5H), 3.05 (d, J = 12.3 Hz, 1H), 2.92 – 2.65 (m, 2H), 2.35 – 1.87 (m, 7H), 1.79 – 1.70 (m, 1H)

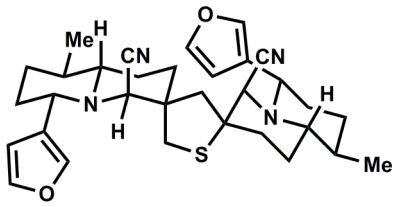
^{13}C NMR (CD_3CN, 151 MHz):

δ 175.04, 169.66, 159.16, 158.93, 134.33, 130.56, 130.03, 125.77, 122.72, 109.52, 64.42, 63.05, 56.79, 49.09, 41.51, 30.27, 26.68, 19.68, 17.97



SI-24: To **SI-23**[2] (0.103 mmol), sodium tetrasulfide (100mg, 0.515 mmol, 5 eq.) was added,

followed by non-anhydrous DMSO (0.35 mL). The red suspension was stirred for 18 hours and monitored by LC/MS for formation of dimers. When >90% of the starting material was gone by LC/MS. The mixture was treated with finely powdered sodium cyanide (0.068 g, 1.4mmol, 20 eq.) and methanol (0.5 mL). The mixture was stirred for ~10 days. The methanol was then removed under a stream of nitrogen and the mixture was diluted with water. The mixture was then extracted with hexanes and ether several times. The organic layer was then washed once with water. The organic layer was then concentrated and the residue was taken up in a small amount of hexanes purified by silica gel preparatory TLC (20x20 cm plate, 250 micron thickness – eluent 15% ether in hexanes). The band at Rf =0.33 is collected and affords 2.5mg of title compound. The bands at Rf = 0.36 and 0.25are not the title compound. The TLC process must be completed quickly (<3 hours) as the desired di-nitrile decomposes slowly on silica gel to a mixture of dihydroxy and monohydroxy-mononitrile compounds.



SI-24

Physical state: colorless solid

Rf = 0.33 (15% ether in hexanes)

[α]D: -57.63 (c = 1.84 mg/ml, CH_2Cl_2)

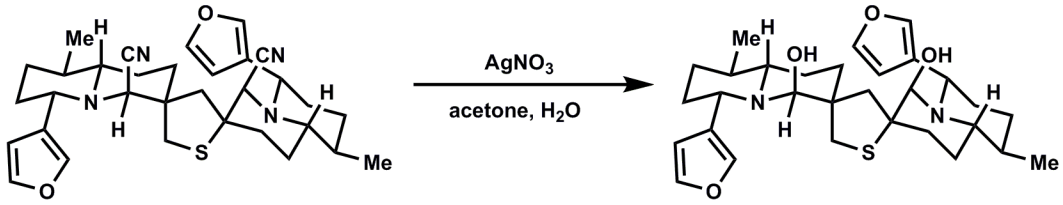
LRMS(APCI) (*m/z*): calculated for $C_{32}H_{40}N_4O_2S$, $[M+H]^+$: 545.7 found 545.7

^{1}H NMR ($CDCl_3$, 400 MHz):

δ 7.42 – 7.26 (m, 4H), 6.47 (s, 1H), 6.32 (s, 1H), 3.91 (s, 1H), 3.66 (s, 1H), 3.35 – 3.32 (m, 2H), 2.99 (d, J = 11.6 Hz, 1H), 2.56 (d, J = 11.6 Hz,1H), 2.11 – 2.03 (m, 1H), 2.03 – 1.94 (m, 1H), 1.94 – 1.09 (m, 20H), 0.99 – 0.85 (m, 6H)

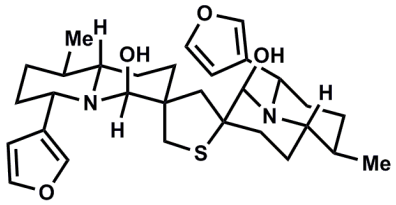
^{13}C NMR ($CDCl_3$, 151 MHz):

δ 143.98, 143.54, 140.34, 140.31, 126.85, 126.72,116.10, 115.74, 109.49, 108.81, 63.10, 62.68, 62.10, 58.81, 57.46, 57.43, 57.32, 51.94, 49.72, 38.46, 37.14, 36.89, 36.62, 34.83, 34.27, 32.92, 31.48, 28.20, 27.58, 18.98, 18.93



SI-24 3a

6,6'-dihydroxyneothiobinupharidine **3a**: To a solution of dinitrile **SI-24** (7 mg,0.013 mmol, 1 eq.) in acetone (1.5 mL) and water (0.5 mL), silver (I) nitrate (109 mg, 0.642 mmol, 50 eq.) was added. The mixture was stirred for 60 hours and monitored by LC/MS for conversion. The reaction mixture was filtered through a plug of grade II neutral alumina (3% w/w water) and rinsed with ether three times followed by 10% ethanol in ether three times. The filtrate was concentrated under a stream of nitrogen and resuspended in ether. This solution was filtered through grade II neutral alumina and rinsed with ether and 10% ethanol in ether three times again. This filtrate was concentrated under a stream of nitrogen and any residual solvent was removed in vacuo to afford 4.2 mg of the title compound.



3a

Physical state: colorless solid

[α]D: -23.43 (c = 3.23 mg/ml, CH_2Cl_2);

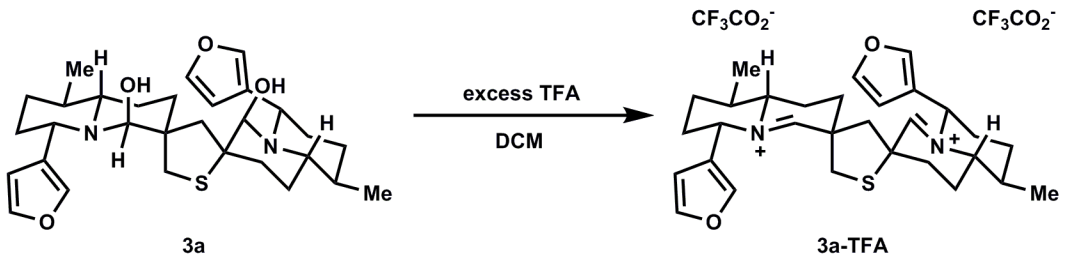
LRMS(APCI) (*m/z*): calculated for $C_{32}H_{40}N_4O_2S$, $[M+H]^+$: 527.7 found 527.7

^{1}H NMR ($CDCl_3$, 600 MHz):

δ 7.38 – 7.34 (m, 4H), 6.55 (s, 1H), 6.36 (s, 1H), 4.28 (d, J = 5.3 Hz, 1H), 4.15 (d, J = 5.3 Hz, 1H), 3.55 – 3.53 (m, 2H), 2.64 (s, 2H), 2.30 – 2.26(m, 1H), 2.21 – 2.18 (m, 1H), 1.92 – 1.87 (m, 1H), 1.82 – 1.05 (m, 19H), 0.88 – 0.85 (m, 6H)

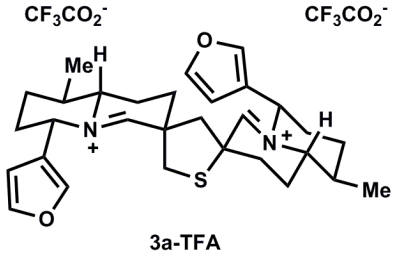
^{13}C NMR ($CDCl_3$, 151 MHz):

δ 143.57, 143.11, 139.54, 139.45, 128.25, 128.22, 110.30, 109.52, 86.55, 85.56, 60.49, 58.27, 57.66, 54.75, 54.32, 51.78, 51.39, 38.50,37.60, 37.16, 35.56, 35.25, 33.55, 33.50, 33.39, 28.94, 28.14, 27.64, 19.19, 19.17



3a 3a-TFA

3a-TFA: The title compound was prepared from **3a** react with excess TFA in DCM at room temperature, removal of TFA with N_2 stream, and dried with high vacuum.



3a-TFA

Physical state: colorless oil

LRMS(APCI) (*m/z*): calculated for $C_{32}H_{40}N_4O_2S$, $[M+H]^+$: 527.7 found 527.7

^{1}H NMR ($CDCl_3$, 600 MHz):

δ 8.11 (s, 1H), 7.84 (s, 1H), 7.68 – 7.63 (m, 3H), 7.57 (s, 1H), 6.59 (s, 1H), 6.51 (s, 1H), 4.93 (d, J = 12.7 Hz, 1H), 4.87 (d, J = 12.7 Hz, 1H), 3.67 – 3.60 (m, 2H), 3.55 – 3.49 (m, 1H), 3.07 (d, J = 12.5 Hz, 1H), 2.66 (d, J = 14.5 Hz, 1H), 2.49 – 2.39 (m, 2H), 2.33 – 2.00 (m, 8H), 1.98 – 1.91 (m, 1H), 1.71 – 1.56 (m, 7H), 1.50 – 1.43 (m, 1H), 1.15 (d, J = 5.6 Hz, 3H), 1.11 (d, J = 6.4 Hz, 3H).

References

1. Norman, M. H.; Heathcock, C. H. Improved synthesis of *N*-benzyl-5-ethyl-1,2,3,4-tetrahydropyridine, *J. Org. Chem.* **1988**, *53*, 3370—3371.
2. Jansen, D. J.; Shenvi, R. A. Synthesis of (−)-Neothiobinupharidine. *J. Am. Chem. Soc.* **2013**, *135*, 1209—1212.

3. Extent of retrodimerization

a) Retrodimerization after 5h with 2.5 mM dimers and 5 mM PhSH in MeOH.

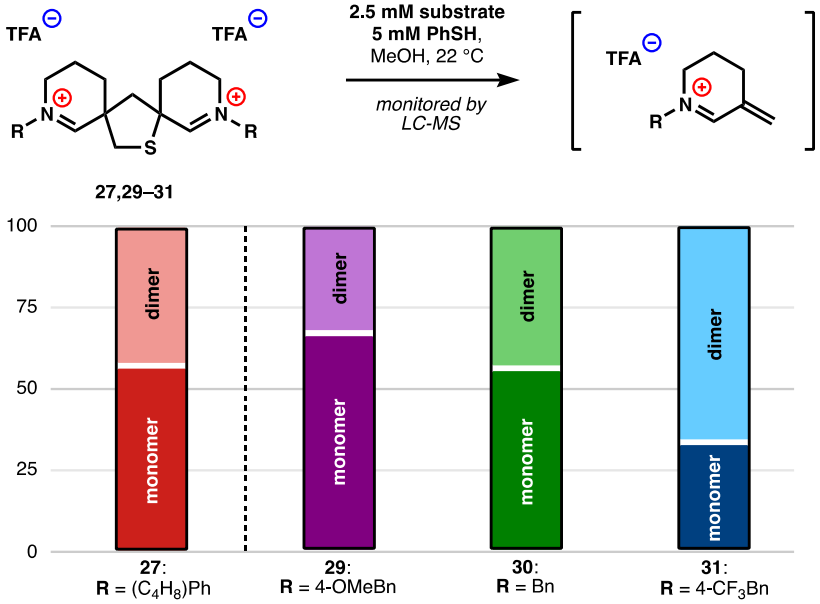


Figure S1. Ratio of dimer and monomer.

b) Retrodimerization after 5 h with 2.5 mM neothiobinupharidine diiminium **3a-TFA** and 5 mM PhSH in MeOH.

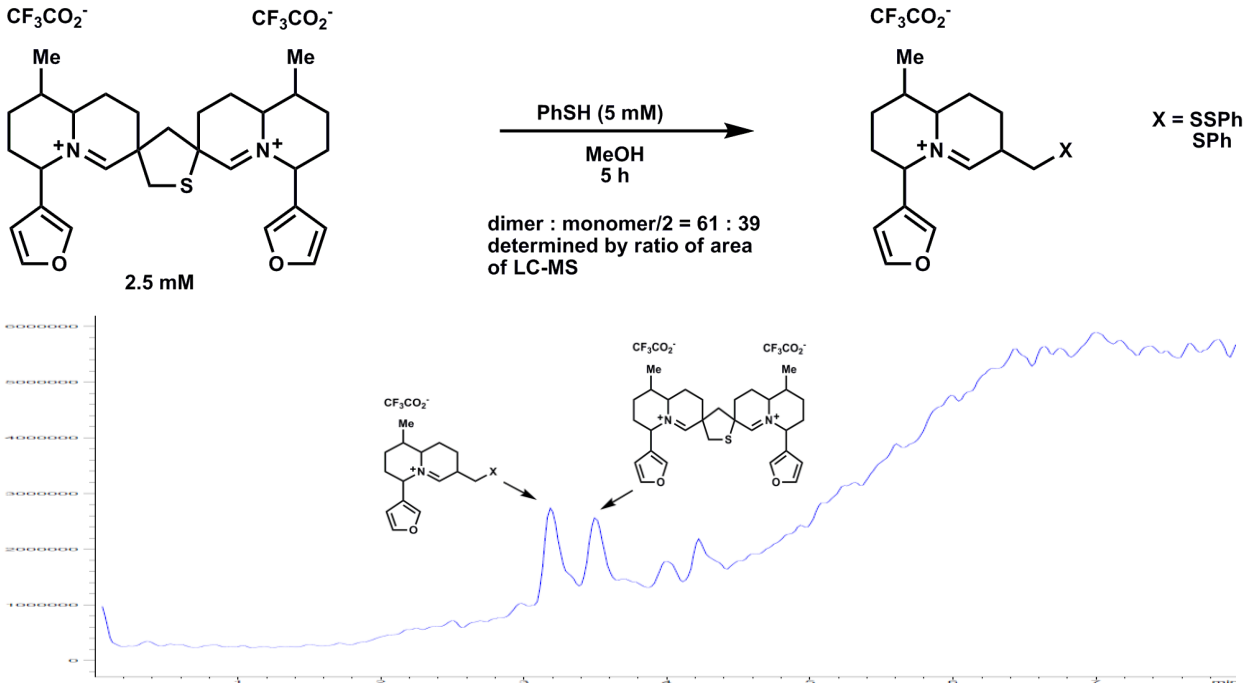


Figure S2. LC-MS after 5h.

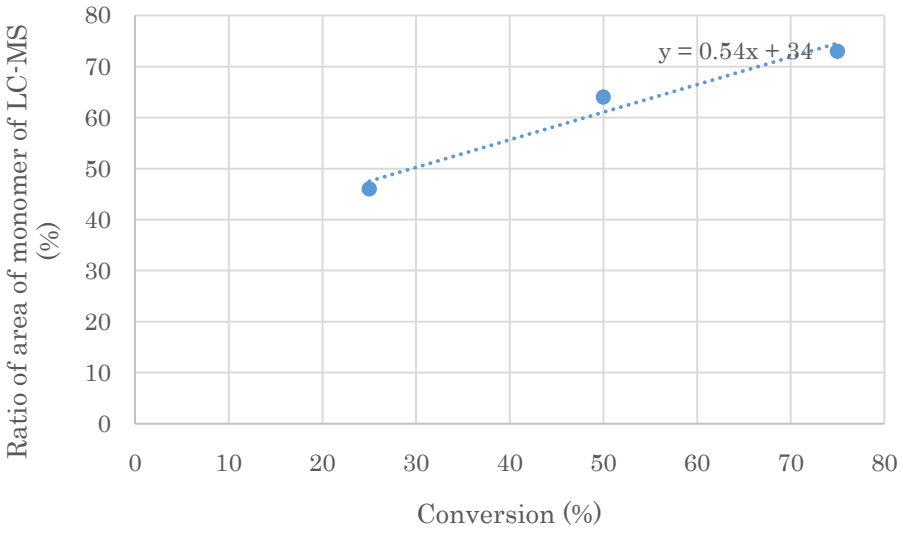


Figure S3. Calibration curve was determined with LC-MS. Horizontal axis: Conversion 25% (monomer : dimer = 2 : 3). Conversion 50% (monomer : dimer = 2 : 1). Conversion 75% (monomer : dimer = 6 : 1). Vertical axis: [area of monomer]/[area of monomer + area of dimer].

c) Retrodimerization after 5 h with 2.5 mM phenylbutyldimer **27** and 5 mM PhSH in MeOH.

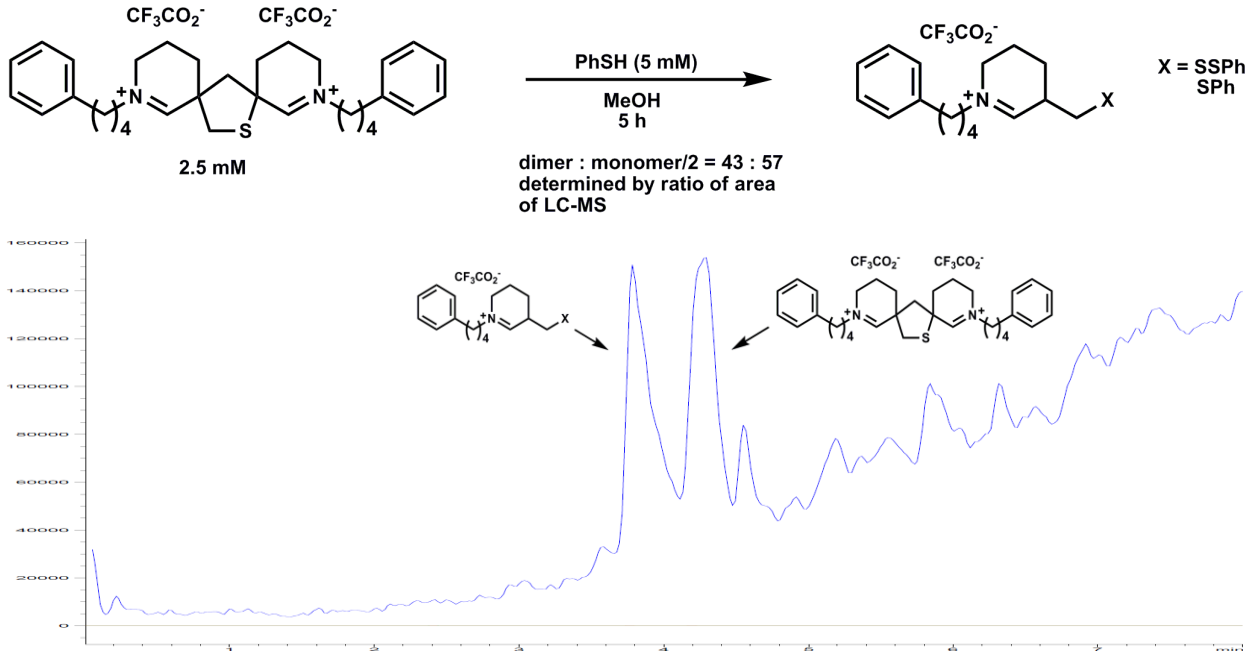


Figure S4. LC-MS after 5 h.

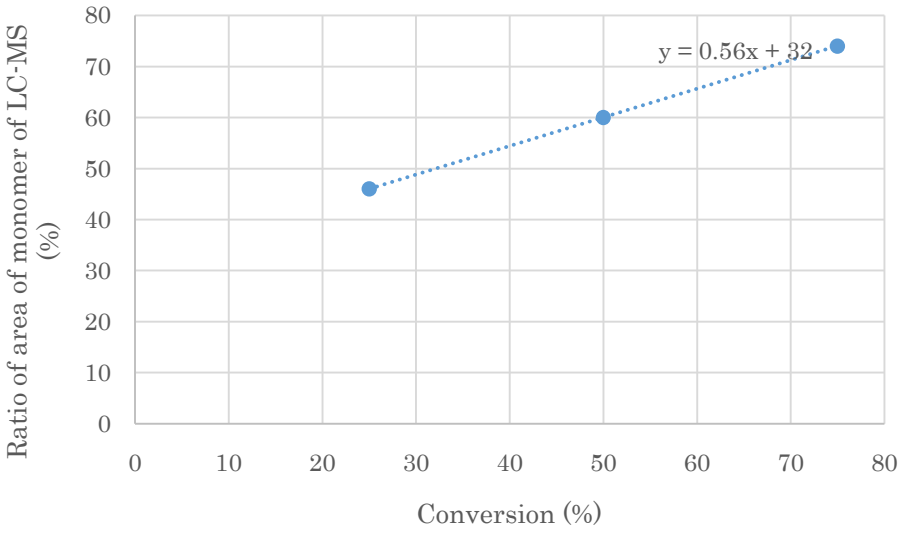


Figure S5. Calibration curve was determined with LC-MS. Horizontal axis: Conversion 25% (monomer : dimer = 2 : 3). Conversion 50% (monomer : dimer = 2 : 1). Conversion 75% (monomer : dimer = 6 : 1). Vertical axis: [area of monomer]/[area of monomer + area of dimer].

d) Retrodimerization after 5 h with 2.5 mM 4-methoxybenzyl dimer **29** and 5 mM PhSH in MeOH.

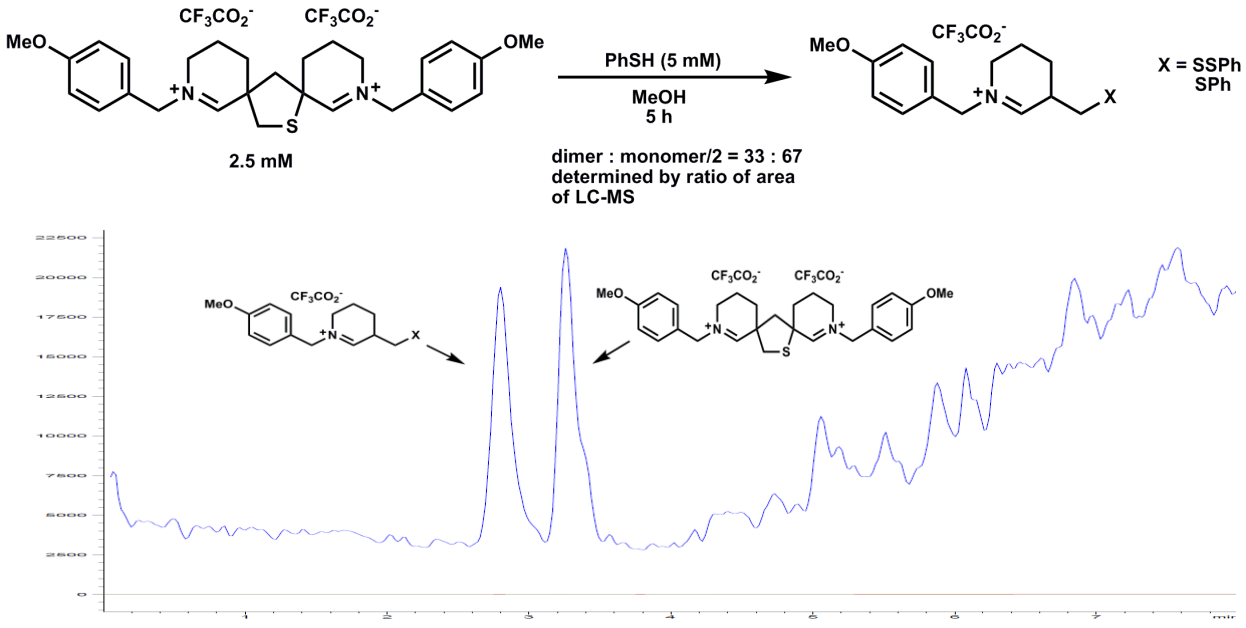


Figure S6. LC-MS after 5 h.

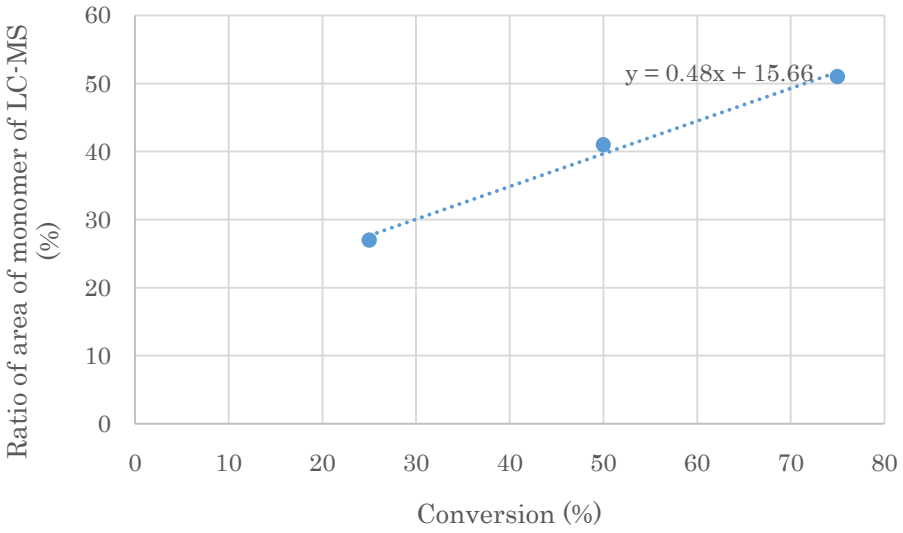


Figure S7. Calibration curve determined with LC-MS. Horizontal axis: Conversion 25% (monomer : dimer = 2 : 3). Conversion 50% (monomer : dimer = 2 : 1). Conversion 75% (monomer : dimer = 6 : 1). Vertical axis: [area of monomer]/[area of monomer + area of dimer].

e) Retrodimerization after 5 h with 2.5 mM benzyldimer **30** and 5 mM PhSH in MeOH.

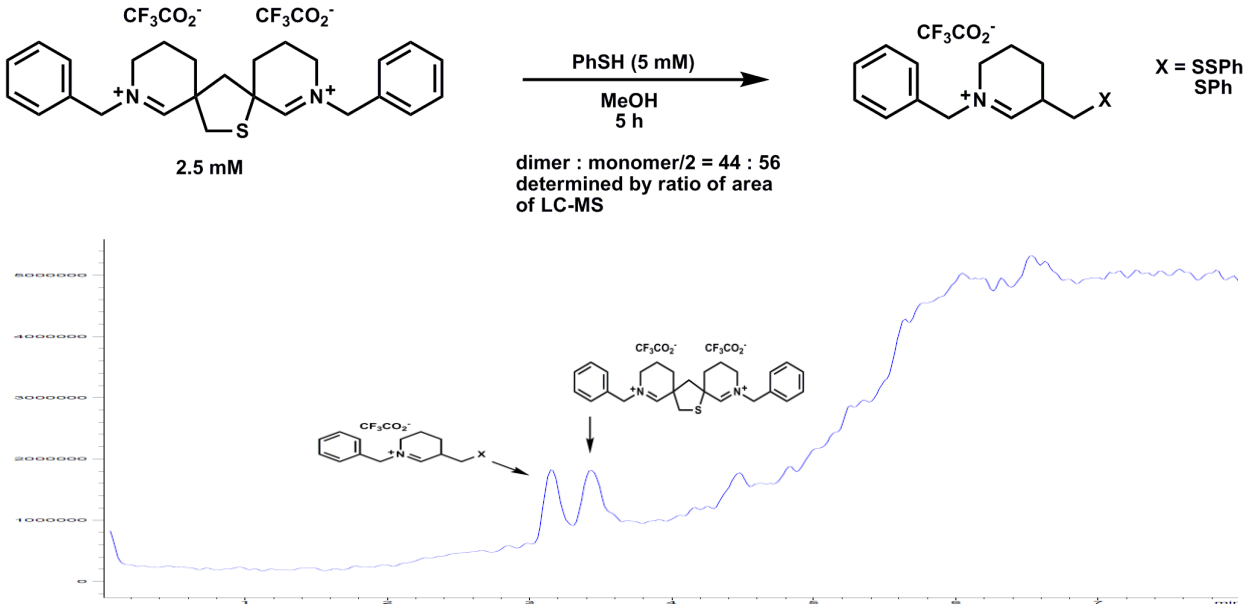


Figure S8. LC-MS after 5 h.

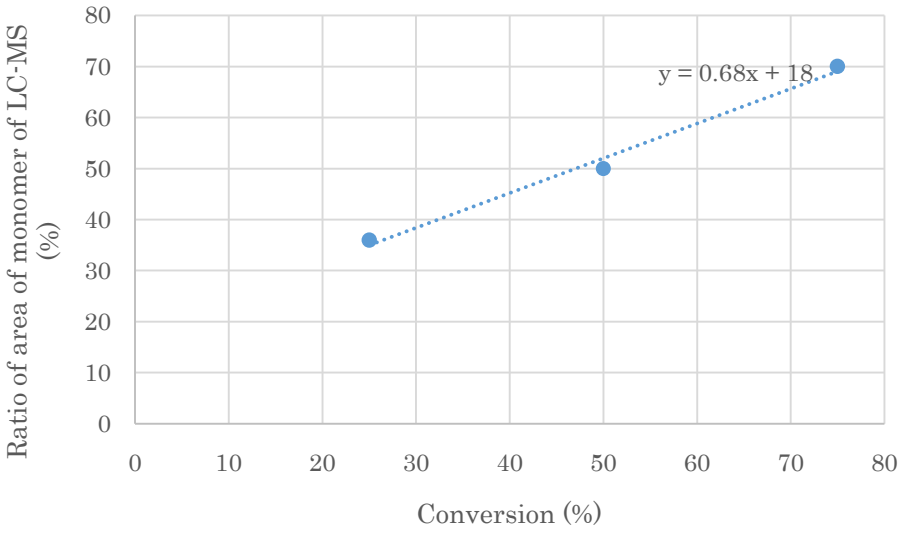


Figure S9. Calibration curve determined with LC-MS. Horizontal axis: Conversion 25% (monomer : dimer = 2 : 3). Conversion 50% (monomer : dimer = 2 : 1). Conversion 75% (monomer : dimer = 6 : 1). Vertical axis: [area of monomer]/[area of monomer + area of dimer].

f) Retrodimerization after 5 h with 2.5 mM 4-trifluoromethylbenzyl dimer **31** and 5 mM PhSH in MeOH.

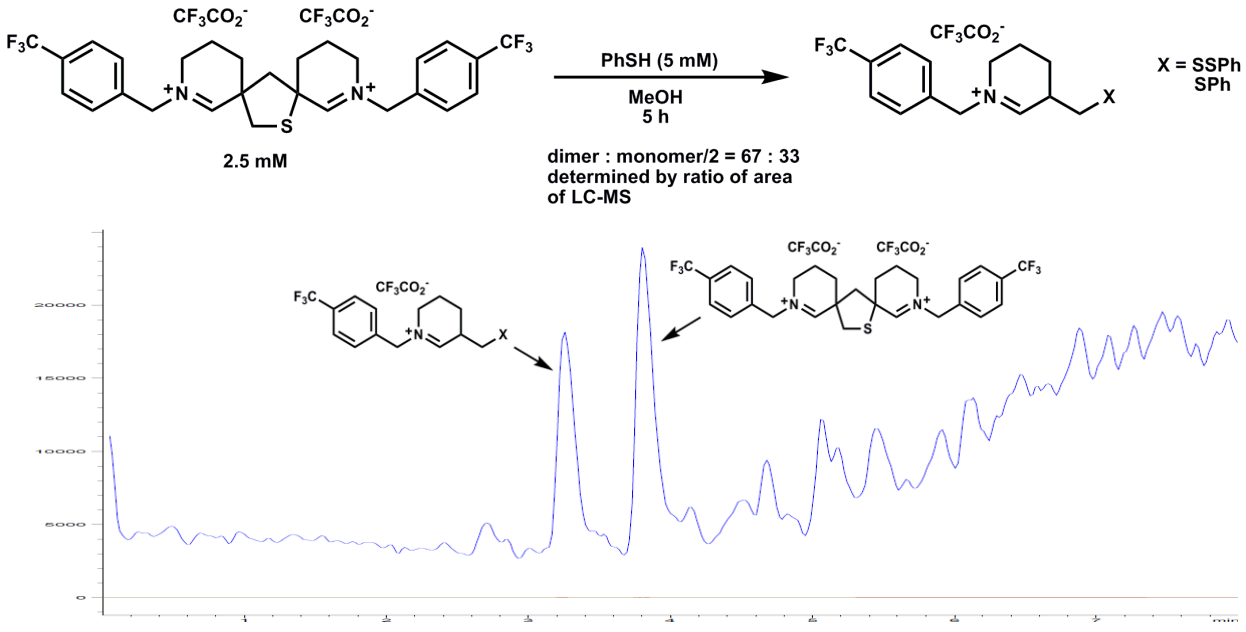


Figure S10. LC-MS after 5 h.

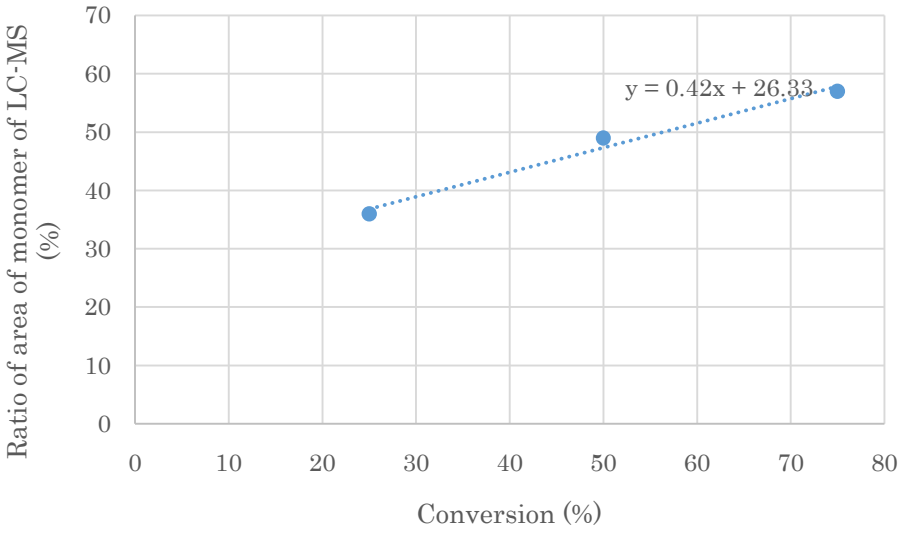


Figure S11. Calibration curve determined with LC-MS. Horizontal axis: Conversion 25% (monomer : dimer = 2 : 3). Conversion 50% (monomer : dimer = 2 : 1). Conversion 75% (monomer : dimer = 6 : 1). Vertical axis: [area of monomer]/[area of monomer + area of dimer].

g) Retrodimerization after 3 d with 0.14 mM neothiobinupharidine diiminium **3a-TFA** and 0.7 mM PhSH in MeOH.

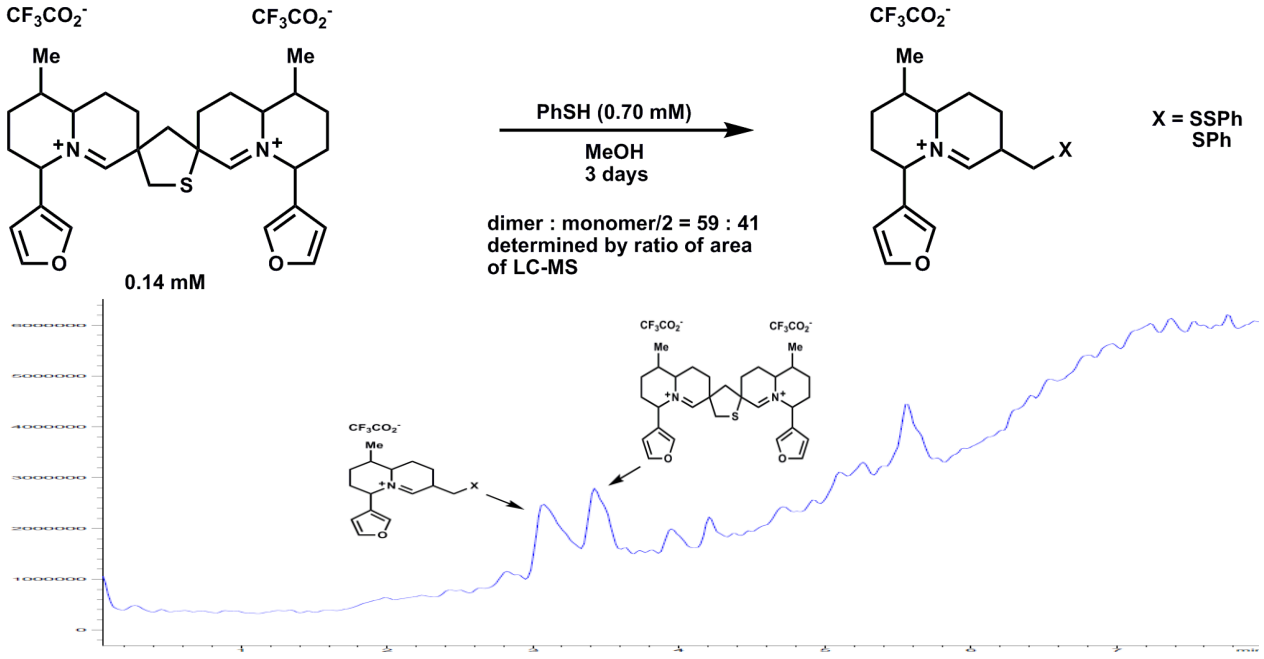


Figure S12. LC-MS after 3 days.

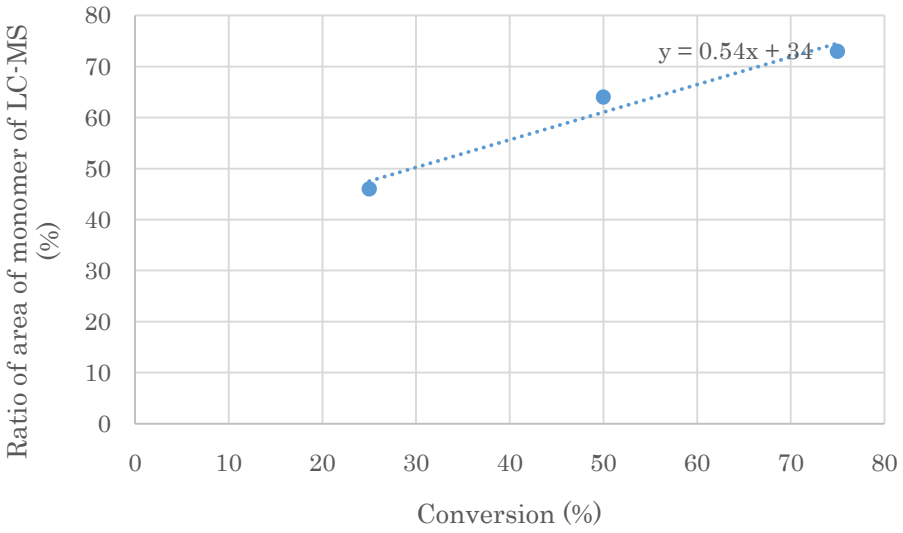


Figure S13. Calibration curve determined with LC-MS. Horizontal axis: Conversion 25% (monomer : dimer = 2 : 3). Conversion 50% (monomer : dimer = 2 : 1). Conversion 75% (monomer : dimer = 6 : 1). Vertical axis: [area of monomer]/[area of monomer + area of dimer].

h) Retrodimerization after 3 d with 0.14 mM phenylbutyldimer **27** and 0.7 mM PhSH in MeOH.

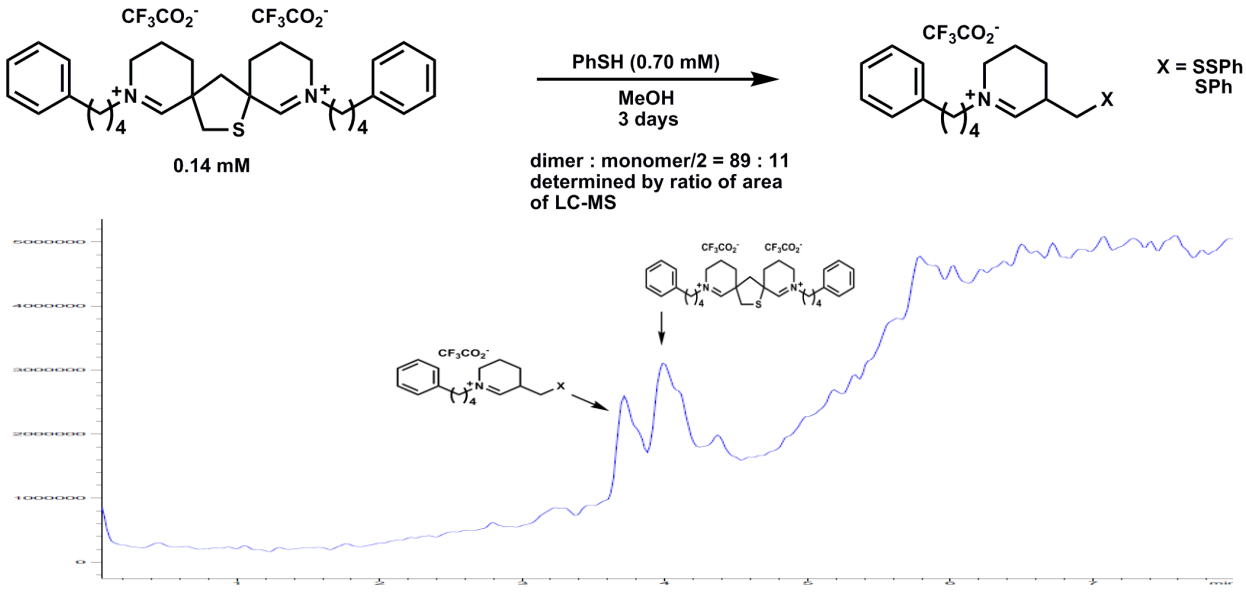


Figure S14. LC-MS after 3 days.

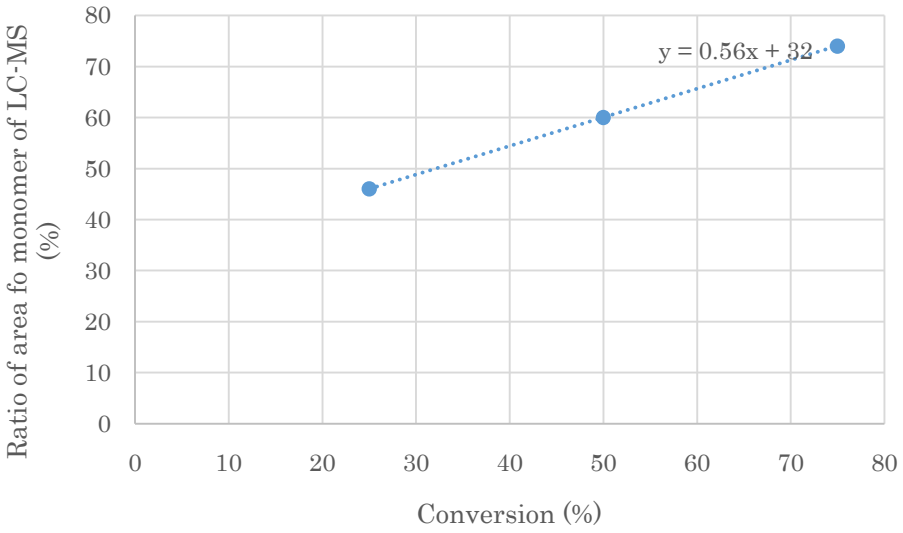


Figure S15. Calibration curve determined with LC-MS. Horizontal axis: Conversion 25% (monomer : dimer = 2 : 3). Conversion 50% (monomer : dimer = 2 : 1). Conversion 75% (monomer : dimer = 6 : 1). Vertical axis: [area of monomer]/[area of monomer + area of dimer].

4. *In Situ* Reaction Monitoring by Transmission IR Spectroscopy

Instrumentation

Transmission IR data were obtained using a Nicolet 7600 FT-IR spectrometer equipped with a liquid nitrogen-cooled MCT detector and a Harrick demountable liquid flow cell with approximate internal volume of 1 mL (TFC-S13-3). The flow cell was constructed using Ge windows (spaced by 25 μm) and angled away from the beam path by 25°. Data collection and analysis was performed using the OMNIC 9 (Thermo Fisher Scientific) software suite.

Experimental Procedure

A solution of thiophenol in THF (4.9 M) was prepared. Approximately 2 mL of this solution was then injected through the IR flow cell and then allowed to sit undisturbed as a background IR spectrum was recorded (64 scans at 4 cm^{-1} resolution). In a separate flask, to iminium substrate was added the thiophenol solution to make 0.049M solution. Upon formation of a homogeneous solution the reaction mixture was injected into the flow cell and excess solution allowed to flow out into a collection vessel. Data acquisition was begun (512 scans per spectrum at 4 cm^{-1} resolution, collected every 1.9 min) and the reaction mixture allowed to evolve undisturbed in the flow cell for at least 24 hrs. At a time varying between 24 and 96 hrs data acquisition was ended and a reaction aliquot taken. At this point sodium cyanoborohydride (5 eq.) was added and the reaction was stirred for 10 minutes (nearly full conversion to disulfide by LC/MS). The reaction was quenched with aqueous HCl to help prevent over reduction (if left for >1 hour, significant amounts of amine thiol is produced). The reaction was concentrated under a stream of nitrogen and residual thiophenol was removed *in vacuo*. The residue was diluted with DCM and washed with aqueous sodium carbonate. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was subjected to column chromatography to afford the disulfide.

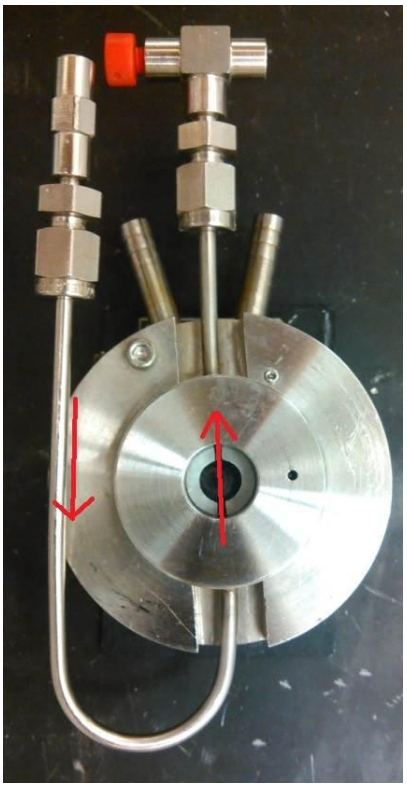


Figure S16. Picture of open flow cell depicting direction of flow, and Teflon spacers

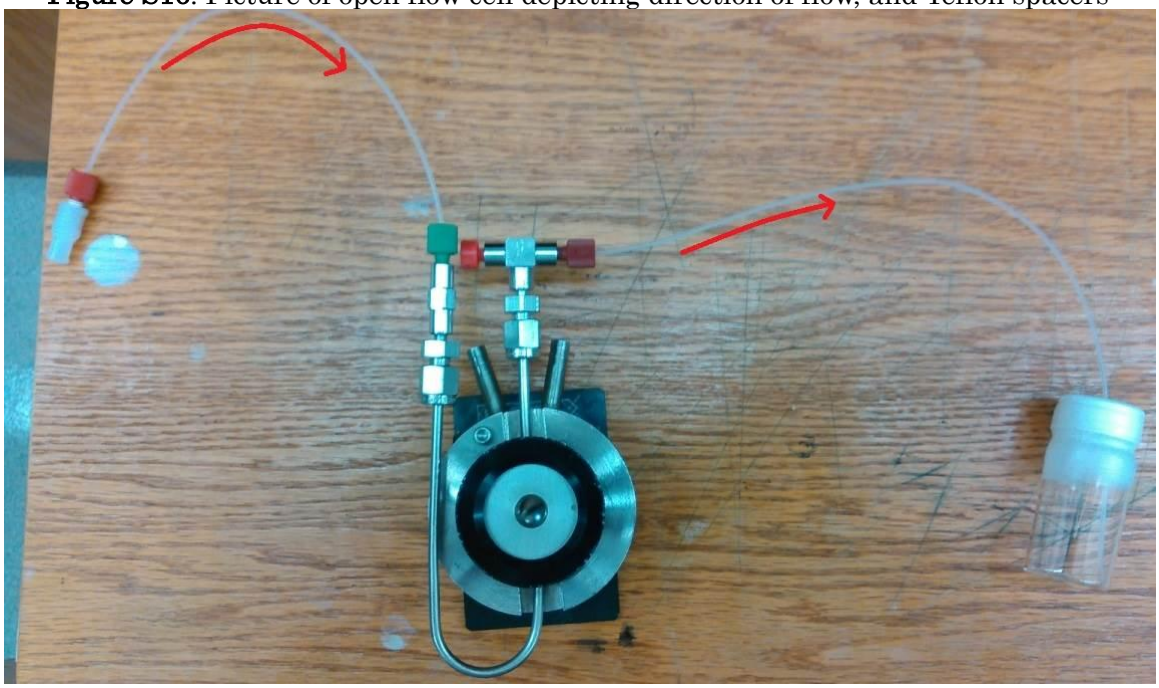


Figure S17. Picture of assembled flow cell apparatus with direction of injection flow indicated by red arrows

Data Analysis

Raw spectra were processed with a second derivative function using a 7 point, 3rd order Savitzky-Golay filter. The relative initial rate of iminium ion consumption was measured by

taking the initial slope of the absorbance vs time curve generated from the peak height of the signal at 1778 cm^{-1}. Slopes were determined using a linear trendline fit to the first stable portion of data. While all experiments were initiated with nominally the same amount of starting material (0.049 M), relative rates were normalized by the initial absorbance at 1778 cm^{-1} to account for experimental errors in the preparation of the reaction mixtures. (This is an appropriate adjustment due to the pseudo-first order kinetics of this reaction run with 100 equivalents of PhSH). Relative initial rates (and their logarithms) were then plotted vs Hammet σ_p parameter[i] and pK_a of the conjugate benzyl ammonium species.[ii]

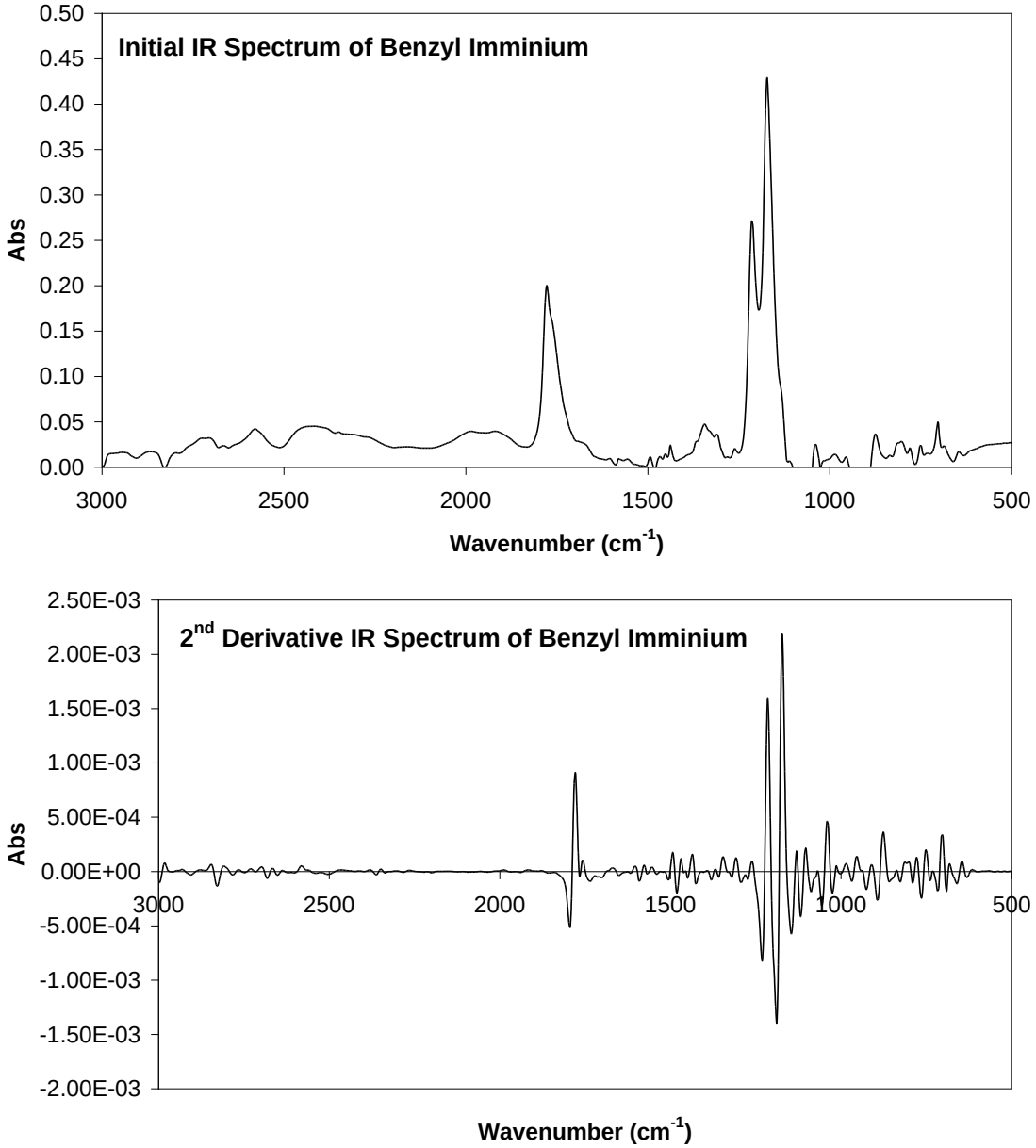


Figure S18. Comparison of raw IR spectrum of benzyl imminum substrate and after second derivative processing (which acts to sharpen the distinction between peaks and eliminate gradual baseline shifts)

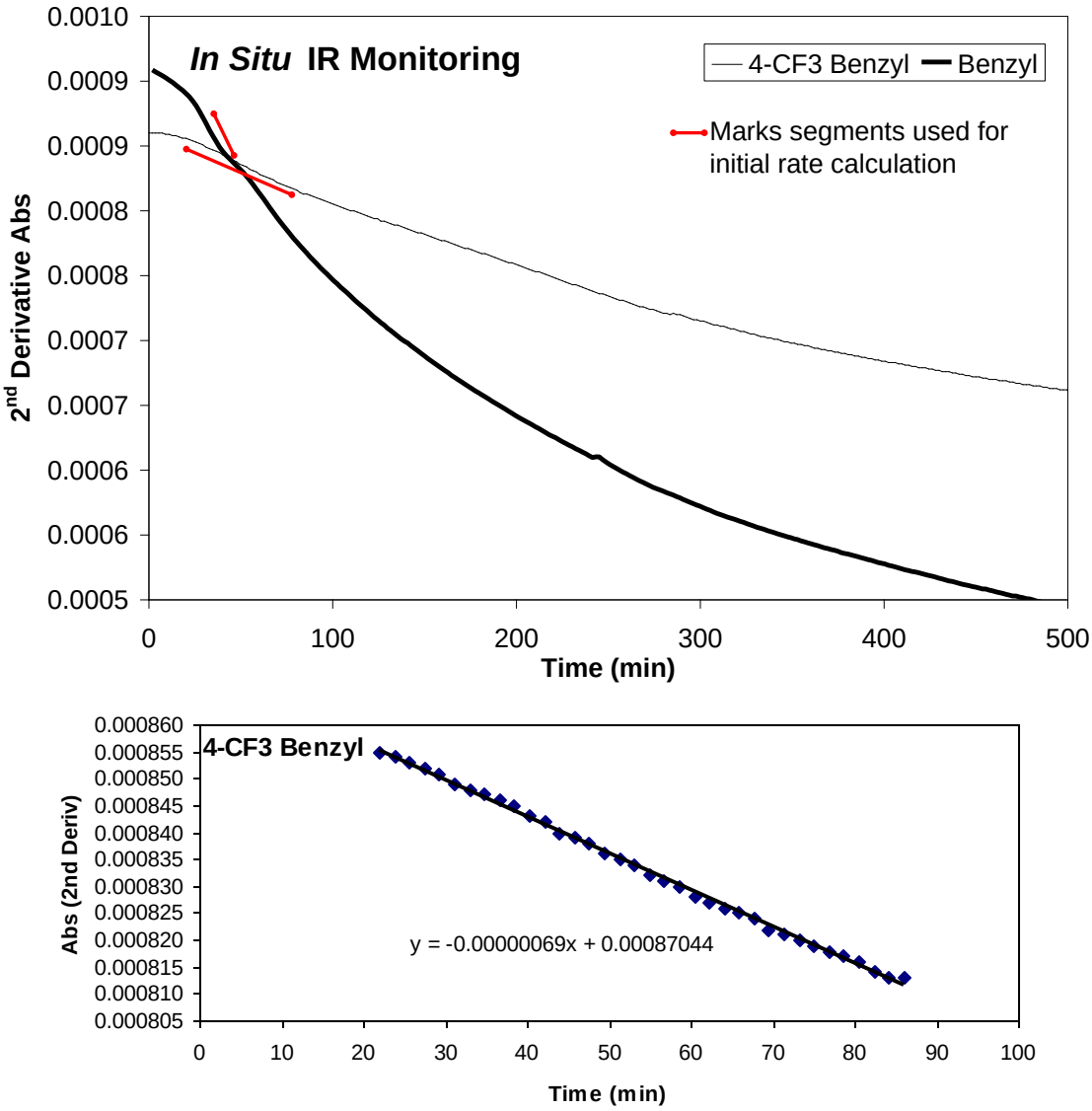


Figure S19. Example showing segment of IR data used for initial rate calculation and linear trendline fit

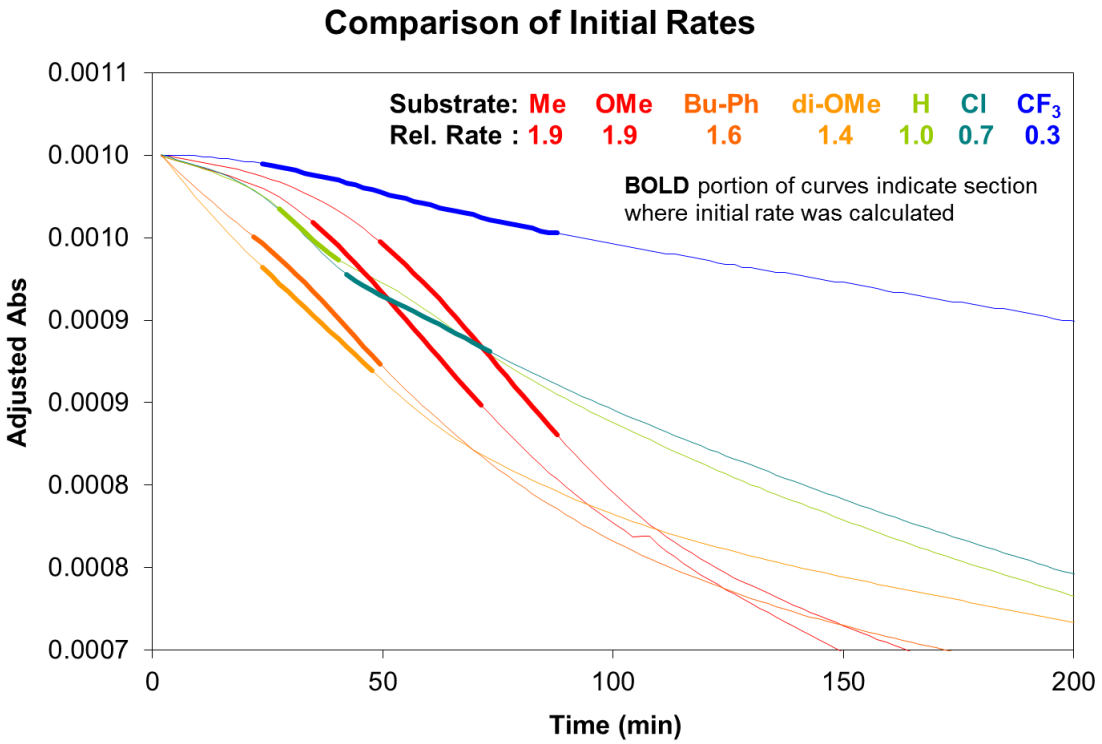


Figure S20. Initial portions of IR decay curves, with the portions used for initial rate determination highlighted in bold

Substrate	Relative Rate	log Relative Rate	Sigma	pKa[a]	pKa[b]
OMe	1.90	0.28	-0.27	9.67	9.30
Me	1.94	0.29	-0.17	9.62	9.21
CF3	0.30	-0.53	0.61	8.95	8.60
Cl	0.65	-0.19	0.23	9.24	8.85
2,4-OMe	1.39	0.14			9.39
H	1.00	0.00	0.00	9.43	9.06
Butyl-Ph	1.64	0.22		10.42	10.66

Table S1. Data used for LFER plots; [a] pKa of conjugate acid at 25C; [b] pKa predicted by ACD ChemSketch

5. X-ray Crystal Data

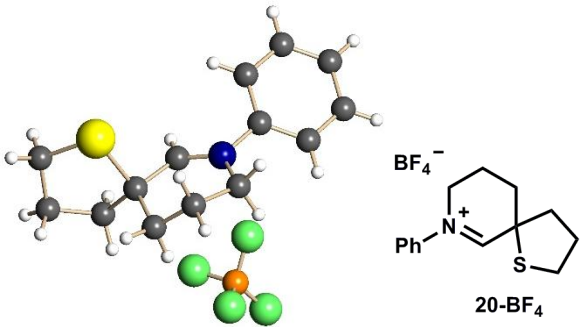


Figure S21. X-ray crystal structure of **20-BF_4**.

Table S2. Crystal data and structure refinement.

Identification code	shenvi43_a	
Empirical formula	C14 H18 B F4 N S	
Formula weight	319.16	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 10.1535(11) Å	α= 90°.
	b = 16.077(2) Å	β= 90°.
	c = 18.3385(14) Å	γ = 90°.
Volume	2993.6(6) $Å^3$	
Z	8	
Density (calculated)	1.416 Mg/m^3	
Absorption coefficient	0.250 mm^{-1}	
F(000)	1328	
Crystal size	0.27 x 0.24 x 0.14 mm^3	
Theta range for data collection	2.221 to 26.382°.	
Index ranges	-12<=h<=12, -20<=k<=15, -22<=l<=22	
Reflections collected	14796	
Independent reflections	3055 [R(int) = 0.0453]	
Completeness to theta = 26.000°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.0932 and 0.0699	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3055 / 67 / 231	
Goodness-of-fit on F^2	1.030	

Final R indices [I>2sigma(I)]	R1 = 0.0871, wR2 = 0.2287
R indices (all data)	R1 = 0.1066, wR2 = 0.2474
Extinction coefficient	n/a
Largest diff. peak and hole	0.809 and -0.271 e.Å^{-3}

Table S3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for shenvi43. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	4759(1)	2929(1)	6234(1)	43(1)
S(2)	4481(9)	4780(5)	6253(5)	43(1)
N(1)	2687(3)	3703(2)	4882(1)	30(1)
C(11)	3756(3)	3860(2)	5233(2)	32(1)
C(10)	3873(4)	3898(2)	6040(2)	40(1)
C(6)	2694(3)	3647(2)	4096(2)	32(1)
C(5)	1695(4)	4010(2)	3698(2)	43(1)
C(1)	3713(4)	3232(2)	3752(2)	43(1)
C(3)	2758(5)	3568(3)	2596(2)	57(1)
C(12)	4829(5)	4631(3)	6280(2)	43(1)
C(8)	1576(4)	3398(3)	6060(2)	62(1)
C(14)	6059(5)	3426(3)	6727(3)	65(1)
C(2)	3728(5)	3200(3)	2996(2)	56(1)
C(13)	5644(5)	4274(2)	6915(2)	63(1)
C(9)	2538(4)	3956(3)	6415(2)	54(1)
C(4)	1736(5)	3966(3)	2943(2)	54(1)
C(7)	1395(3)	3593(3)	5255(2)	42(1)
F(3)	3297(8)	6431(6)	5665(6)	86(2)
F(6)	3415(11)	6154(10)	5396(7)	64(2)
F(2)	2546(19)	6888(11)	5111(10)	60(3)
F(8)	2343(12)	5496(5)	4798(5)	69(2)
F(4)	1631(10)	5674(7)	4600(5)	97(3)
F(5)	1357(3)	5885(2)	5779(2)	85(1)
F(1)	1774(5)	6830(2)	4926(2)	83(1)
F(7)	3265(9)	5608(6)	5077(6)	109(3)
B(1)	2176(5)	6113(3)	5229(3)	50(1)

Table S4. Bond lengths [Å] and angles [°].

S(1)-C(10)	1.834(4)
S(1)-C(14)	1.789(4)
S(2)-C(10)	1.596(10)
N(1)-C(11)	1.287(4)
N(1)-C(6)	1.445(4)
N(1)-C(7)	1.489(4)
C(11)-H(11)	0.9300
C(11)-C(10)	1.486(4)
C(10)-C(12)	1.590(6)
C(10)-C(9)	1.523(5)
C(6)-C(5)	1.379(5)
C(6)-C(1)	1.384(5)
C(5)-H(5)	0.9300
C(5)-C(4)	1.387(5)
C(1)-H(1)	0.9300
C(1)-C(2)	1.387(5)
C(3)-H(3)	0.9300
C(3)-C(2)	1.363(6)
C(3)-C(4)	1.375(7)
C(12)-H(12A)	0.9700
C(12)-H(12B)	0.9700
C(12)-C(13)	1.539(5)
C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
C(8)-C(9)	1.476(6)
C(8)-C(7)	1.521(6)
C(14)-H(14A)	0.9700
C(14)-H(14B)	0.9700
C(14)-C(13)	1.467(6)
C(2)-H(2)	0.9300
C(13)-H(13A)	0.9700
C(13)-H(13B)	0.9700
C(9)-H(9A)	0.9700
C(9)-H(9B)	0.9700

C(4)-H(4)	0.9300
C(7)-H(7A)	0.9700
C(7)-H(7B)	0.9700
F(3)-B(1)	1.483(10)
F(6)-F(2)	1.56(2)
F(6)-B(1)	1.297(13)
F(2)-B(1)	1.319(18)
F(8)-B(1)	1.280(9)
F(4)-B(1)	1.461(10)
F(5)-B(1)	1.359(6)
F(1)-B(1)	1.343(6)
F(7)-B(1)	1.400(8)

C(14)-S(1)-C(10)	94.58(19)
C(11)-N(1)-C(6)	120.4(3)
C(11)-N(1)-C(7)	122.5(3)
C(6)-N(1)-C(7)	117.1(3)
N(1)-C(11)-H(11)	117.5
N(1)-C(11)-C(10)	124.9(3)
C(10)-C(11)-H(11)	117.5
C(11)-C(10)-S(1)	101.4(2)
C(11)-C(10)-S(2)	108.1(4)
C(11)-C(10)-C(12)	110.8(3)
C(11)-C(10)-C(9)	112.4(3)
C(12)-C(10)-S(1)	106.1(3)
C(9)-C(10)-S(1)	113.6(3)
C(9)-C(10)-S(2)	100.3(4)
C(9)-C(10)-C(12)	111.9(3)
C(5)-C(6)-N(1)	119.9(3)
C(5)-C(6)-C(1)	120.8(3)
C(1)-C(6)-N(1)	119.3(3)
C(6)-C(5)-H(5)	120.5
C(6)-C(5)-C(4)	119.0(4)
C(4)-C(5)-H(5)	120.5
C(6)-C(1)-H(1)	120.6
C(6)-C(1)-C(2)	118.8(4)

C(2)-C(1)-H(1)	120.6
C(2)-C(3)-H(3)	120.1
C(2)-C(3)-C(4)	119.9(4)
C(4)-C(3)-H(3)	120.1
C(10)-C(12)-H(12A)	110.7
C(10)-C(12)-H(12B)	110.7
H(12A)-C(12)-H(12B)	108.8
C(13)-C(12)-C(10)	105.1(3)
C(13)-C(12)-H(12A)	110.7
C(13)-C(12)-H(12B)	110.7
H(8A)-C(8)-H(8B)	107.8
C(9)-C(8)-H(8A)	109.1
C(9)-C(8)-H(8B)	109.1
C(9)-C(8)-C(7)	112.5(4)
C(7)-C(8)-H(8A)	109.1
C(7)-C(8)-H(8B)	109.1
S(1)-C(14)-H(14A)	109.9
S(1)-C(14)-H(14B)	109.9
H(14A)-C(14)-H(14B)	108.3
C(13)-C(14)-S(1)	108.8(3)
C(13)-C(14)-H(14A)	109.9
C(13)-C(14)-H(14B)	109.9
C(1)-C(2)-H(2)	119.5
C(3)-C(2)-C(1)	120.9(4)
C(3)-C(2)-H(2)	119.5
C(12)-C(13)-H(13A)	109.9
C(12)-C(13)-H(13B)	109.9
C(14)-C(13)-C(12)	108.9(3)
C(14)-C(13)-H(13A)	109.9
C(14)-C(13)-H(13B)	109.9
H(13A)-C(13)-H(13B)	108.3
C(10)-C(9)-H(9A)	109.5
C(10)-C(9)-H(9B)	109.5
C(8)-C(9)-C(10)	110.7(3)
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5

H(9A)-C(9)-H(9B)	108.1
C(5)-C(4)-H(4)	119.7
C(3)-C(4)-C(5)	120.6(4)
C(3)-C(4)-H(4)	119.7
N(1)-C(7)-C(8)	111.3(3)
N(1)-C(7)-H(7A)	109.4
N(1)-C(7)-H(7B)	109.4
C(8)-C(7)-H(7A)	109.4
C(8)-C(7)-H(7B)	109.4
H(7A)-C(7)-H(7B)	108.0
B(1)-F(6)-F(2)	53.9(8)
B(1)-F(2)-F(6)	52.6(8)
F(6)-B(1)-F(2)	73.4(11)
F(6)-B(1)-F(4)	125.4(8)
F(6)-B(1)-F(5)	115.5(7)
F(2)-B(1)-F(4)	115.9(10)
F(2)-B(1)-F(5)	123.4(8)
F(8)-B(1)-F(3)	119.9(7)
F(8)-B(1)-F(5)	109.2(5)
F(8)-B(1)-F(1)	116.8(7)
F(5)-B(1)-F(3)	99.3(6)
F(5)-B(1)-F(4)	102.9(5)
F(5)-B(1)-F(7)	118.3(5)
F(1)-B(1)-F(3)	99.3(5)
F(1)-B(1)-F(5)	110.7(4)

Symmetry transformations used to generate equivalent atoms:

Table S5. Anisotropic displacement parameters ($Å^2 x\ 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	58(1)	36(1)	35(1)	2(1)	-6(1)	3(1)
S(2)	58(1)	36(1)	35(1)	2(1)	-6(1)	3(1)
N(1)	28(1)	32(1)	30(1)	3(1)	2(1)	2(1)
C(11)	30(2)	37(2)	29(2)	6(1)	1(1)	1(1)
C(10)	40(2)	50(2)	28(2)	6(1)	1(1)	-2(2)
C(6)	37(2)	32(2)	29(2)	1(1)	0(1)	-5(1)
C(5)	41(2)	48(2)	41(2)	0(2)	-9(2)	0(2)
C(1)	50(2)	42(2)	38(2)	-2(2)	2(2)	4(2)
C(3)	87(3)	53(2)	30(2)	-1(2)	-2(2)	-25(2)
C(12)	58(1)	36(1)	35(1)	2(1)	-6(1)	3(1)
C(8)	51(2)	93(3)	43(2)	-3(2)	17(2)	-17(2)
C(14)	78(3)	53(3)	64(3)	10(2)	-37(2)	-2(2)
C(2)	68(3)	56(2)	43(2)	-11(2)	14(2)	-8(2)
C(13)	85(3)	42(2)	61(3)	-4(2)	-38(2)	0(2)
C(9)	55(3)	74(3)	35(2)	-1(2)	7(2)	0(2)
C(4)	64(3)	54(2)	42(2)	7(2)	-21(2)	-12(2)
C(7)	27(2)	61(2)	40(2)	0(2)	6(1)	-6(2)
F(3)	63(3)	75(5)	119(5)	-18(4)	-12(3)	0(3)
F(6)	43(3)	72(6)	77(6)	-12(4)	10(3)	7(3)
F(2)	48(5)	58(3)	73(7)	-2(3)	13(5)	-1(3)
F(8)	72(5)	47(3)	86(4)	-5(3)	12(4)	-1(3)
F(4)	76(5)	114(6)	100(4)	-33(4)	0(3)	-16(4)
F(5)	59(2)	104(2)	90(2)	31(2)	18(1)	9(2)
F(1)	82(3)	66(2)	101(3)	26(2)	10(2)	9(2)
F(7)	81(4)	94(5)	153(7)	35(5)	48(4)	39(4)
B(1)	43(2)	43(2)	64(2)	4(1)	9(2)	0(1)

Table S6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3).

	x	y	z	U(eq)
H(11)	4513	3958	4960	39
H(5)	1005	4281	3932	52
H(1)	4376	2978	4022	52
H(3)	2786	3549	2089	68
H(12A)	5397	4795	5880	52
H(12B)	4328	5112	6439	52
H(8A)	734	3449	6306	75
H(8B)	1871	2827	6112	75
H(14A)	6253	3116	7168	78
H(14B)	6849	3444	6431	78
H(2)	4409	2925	2758	67
H(13A)	6411	4620	7001	76
H(13B)	5119	4265	7356	76
H(9A)	2629	3803	6924	65
H(9B)	2221	4524	6392	65
H(4)	1067	4208	2669	64
H(7A)	914	3143	5024	51
H(7B)	879	4097	5203	51

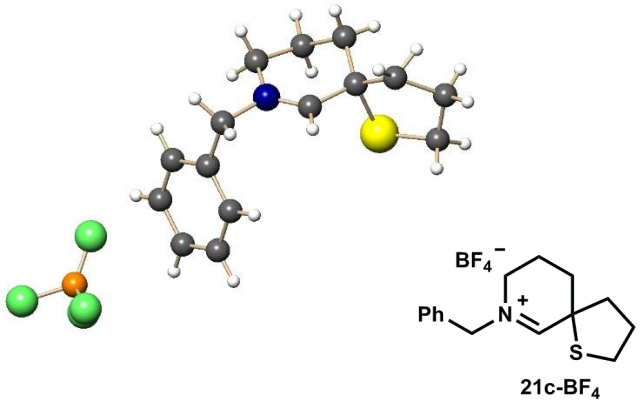


Figure S22. X-ray crystal structure of **21c-BF_4.**

Table S7. Crystal data and structure refinement.

Identification code	shenvi41	
Empirical formula	C15 H20 B F4 N S	
Formula weight	333.19	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 8.6004(6) Å	α= 90°.
	b = 18.4413(14) Å	β= 106.254(3)°.
	c = 10.5940(6) Å	γ = 90°.
Volume	1613.08(19) $Å^3$	
Z	4	
Density (calculated)	1.372 Mg/m^3	
Absorption coefficient	0.235 mm^{-1}	
F(000)	696	
Crystal size	0.37 x 0.33 x 0.29 mm^3	
Theta range for data collection	2.209 to 26.381°.	
Index ranges	-10<=h<=10, -22<=k<=23, -12<=l<=13	
Reflections collected	12564	
Independent reflections	3302 [R(int) = 0.0418]	
Completeness to theta = 26.000°	100.0 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.1660 and 0.1207	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	3302 / 60 / 241
Goodness-of-fit on F^2	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0447, wR2 = 0.0972
R indices (all data)	R1 = 0.0661, wR2 = 0.1090
Extinction coefficient	n/a
Largest diff. peak and hole	0.476 and -0.295 e.$Å^{-3}$

Table S8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	3050(1)	5631(1)	338(1)	29(1)
F(8)	1260(20)	5976(10)	5390(20)	35(1)
F(6)	3293(17)	5564(6)	7194(11)	32(2)
F(1)	3390(20)	5265(11)	5583(14)	40(3)
N(1)	1900(2)	4840(1)	2867(2)	20(1)
C(12)	3120(2)	5175(1)	2677(2)	22(1)
F(3)	3432(16)	6662(7)	5761(14)	73(3)
C(6)	1642(2)	3521(1)	2469(2)	22(1)
C(7)	2094(3)	4112(1)	3496(2)	25(1)
C(2)	-329(3)	2710(1)	1117(2)	29(1)
C(11)	3027(3)	5894(1)	2030(2)	26(1)
C(1)	79(3)	3240(1)	2084(2)	26(1)
C(3)	821(3)	2460(1)	537(2)	32(1)
C(8)	231(3)	5141(1)	2512(2)	27(1)
C(5)	2789(3)	3268(1)	1877(2)	28(1)
C(4)	2373(3)	2738(1)	906(2)	34(1)
C(10)	1486(3)	6288(1)	2048(2)	34(1)
C(9)	41(3)	5785(1)	1602(2)	34(1)
C(15)	4571(3)	6343(2)	2574(2)	44(1)
C(13)	4860(3)	6146(2)	383(3)	39(1)
B(1)	2901(3)	5980(2)	6033(2)	28(1)
C(14A)	5734(5)	6183(2)	1921(4)	35(1)
C(14)	5094(8)	6679(4)	1430(6)	32(2)
F(4)	3044(5)	6725(2)	6308(9)	58(2)
F(5)	3402(10)	5798(6)	7319(6)	45(2)
F(7)	1283(11)	5815(6)	5448(13)	35(1)
F(2)	3861(2)	5727(2)	5303(2)	55(1)

Table S9. Bond lengths [Å] and angles [°].

S(1)-C(11)	1.862(2)
S(1)-C(13)	1.812(2)
F(8)-B(1)	1.382(16)
F(6)-B(1)	1.407(9)
F(1)-B(1)	1.501(15)
N(1)-C(12)	1.281(3)
N(1)-C(7)	1.488(3)
N(1)-C(8)	1.486(3)
C(12)-H(12)	0.9500
C(12)-C(11)	1.484(3)
F(3)-B(1)	1.396(7)
C(6)-C(7)	1.512(3)
C(6)-C(1)	1.391(3)
C(6)-C(5)	1.390(3)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(2)-H(2)	0.9500
C(2)-C(1)	1.388(3)
C(2)-C(3)	1.381(3)
C(11)-C(10)	1.517(3)
C(11)-C(15)	1.534(3)
C(1)-H(1)	0.9500
C(3)-H(3)	0.9500
C(3)-C(4)	1.380(3)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(8)-C(9)	1.509(3)
C(5)-H(5)	0.9500
C(5)-C(4)	1.391(3)
C(4)-H(4)	0.9500
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(10)-C(9)	1.516(3)
C(9)-H(9A)	0.9900

C(9)-H(9B)	0.9900
C(15)-H(15C)	0.9900
C(15)-H(15D)	0.9900
C(15)-H(15B)	0.9900
C(15)-H(15A)	0.9900
C(15)-C(14A)	1.397(5)
C(15)-C(14)	1.536(6)
C(13)-H(13C)	0.9900
C(13)-H(13D)	0.9900
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(13)-C(14A)	1.593(5)
C(13)-C(14)	1.452(6)
B(1)-F(4)	1.402(4)
B(1)-F(5)	1.351(6)
B(1)-F(7)	1.389(9)
B(1)-F(2)	1.362(3)
C(14A)-H(14A)	0.9900
C(14A)-H(14B)	0.9900
C(14)-H(14C)	0.9900
C(14)-H(14D)	0.9900

C(13)-S(1)-C(11)	94.49(11)
C(12)-N(1)-C(7)	120.76(18)
C(12)-N(1)-C(8)	123.79(18)
C(8)-N(1)-C(7)	115.44(17)
N(1)-C(12)-H(12)	117.9
N(1)-C(12)-C(11)	124.25(19)
C(11)-C(12)-H(12)	117.9
C(1)-C(6)-C(7)	120.79(19)
C(5)-C(6)-C(7)	119.73(19)
C(5)-C(6)-C(1)	119.5(2)
N(1)-C(7)-C(6)	110.73(16)
N(1)-C(7)-H(7A)	109.5
N(1)-C(7)-H(7B)	109.5
C(6)-C(7)-H(7A)	109.5

C(6)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	108.1
C(1)-C(2)-H(2)	120.0
C(3)-C(2)-H(2)	120.0
C(3)-C(2)-C(1)	119.9(2)
C(12)-C(11)-S(1)	101.49(14)
C(12)-C(11)-C(10)	110.84(18)
C(12)-C(11)-C(15)	112.30(19)
C(10)-C(11)-S(1)	112.45(15)
C(10)-C(11)-C(15)	113.8(2)
C(15)-C(11)-S(1)	105.13(15)
C(6)-C(1)-H(1)	119.9
C(2)-C(1)-C(6)	120.2(2)
C(2)-C(1)-H(1)	119.9
C(2)-C(3)-H(3)	119.8
C(4)-C(3)-C(2)	120.4(2)
C(4)-C(3)-H(3)	119.8
N(1)-C(8)-H(8A)	109.1
N(1)-C(8)-H(8B)	109.1
N(1)-C(8)-C(9)	112.29(18)
H(8A)-C(8)-H(8B)	107.9
C(9)-C(8)-H(8A)	109.1
C(9)-C(8)-H(8B)	109.1
C(6)-C(5)-H(5)	119.9
C(6)-C(5)-C(4)	120.1(2)
C(4)-C(5)-H(5)	119.9
C(3)-C(4)-C(5)	119.9(2)
C(3)-C(4)-H(4)	120.0
C(5)-C(4)-H(4)	120.0
C(11)-C(10)-H(10A)	109.6
C(11)-C(10)-H(10B)	109.6
H(10A)-C(10)-H(10B)	108.1
C(9)-C(10)-C(11)	110.21(19)
C(9)-C(10)-H(10A)	109.6
C(9)-C(10)-H(10B)	109.6
C(8)-C(9)-C(10)	110.45(19)

C(8)-C(9)-H(9A)	109.6
C(8)-C(9)-H(9B)	109.6
C(10)-C(9)-H(9A)	109.6
C(10)-C(9)-H(9B)	109.6
H(9A)-C(9)-H(9B)	108.1
C(11)-C(15)-H(15C)	109.4
C(11)-C(15)-H(15D)	109.4
C(11)-C(15)-H(15B)	109.8
C(11)-C(15)-H(15A)	109.8
C(11)-C(15)-C(14)	109.6(3)
H(15C)-C(15)-H(15D)	108.0
H(15B)-C(15)-H(15A)	108.2
C(14A)-C(15)-C(11)	111.4(2)
C(14A)-C(15)-H(15C)	109.4
C(14A)-C(15)-H(15D)	109.4
C(14)-C(15)-H(15B)	109.8
C(14)-C(15)-H(15A)	109.8
S(1)-C(13)-H(13C)	111.4
S(1)-C(13)-H(13D)	111.4
S(1)-C(13)-H(13A)	110.1
S(1)-C(13)-H(13B)	110.1
H(13C)-C(13)-H(13D)	109.3
H(13A)-C(13)-H(13B)	108.4
C(14A)-C(13)-S(1)	101.86(19)
C(14A)-C(13)-H(13C)	111.4
C(14A)-C(13)-H(13D)	111.4
C(14)-C(13)-S(1)	108.0(3)
C(14)-C(13)-H(13A)	110.1
C(14)-C(13)-H(13B)	110.1
F(8)-B(1)-F(6)	113.0(11)
F(8)-B(1)-F(1)	100.0(11)
F(8)-B(1)-F(3)	104.5(8)
F(6)-B(1)-F(1)	77.2(8)
F(3)-B(1)-F(6)	131.3(9)
F(3)-B(1)-F(1)	126.1(14)
F(5)-B(1)-F(4)	92.9(8)

F(5)-B(1)-F(7)	113.1(7)
F(5)-B(1)-F(2)	114.5(4)
F(7)-B(1)-F(4)	109.1(5)
F(2)-B(1)-F(4)	114.9(5)
F(2)-B(1)-F(7)	111.2(6)
C(15)-C(14A)-C(13)	108.5(3)
C(15)-C(14A)-H(14A)	110.0
C(15)-C(14A)-H(14B)	110.0
C(13)-C(14A)-H(14A)	110.0
C(13)-C(14A)-H(14B)	110.0
H(14A)-C(14A)-H(14B)	108.4
C(15)-C(14)-H(14C)	109.9
C(15)-C(14)-H(14D)	109.9
C(13)-C(14)-C(15)	108.7(4)
C(13)-C(14)-H(14C)	109.9
C(13)-C(14)-H(14D)	109.9
H(14C)-C(14)-H(14D)	108.3

Symmetry transformations used to generate equivalent atoms:

Table S10. Anisotropic displacement parameters ($Å^2 x\ 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	32(1)	37(1)	17(1)	-4(1)	6(1)	-4(1)
F(8)	21(1)	51(4)	29(1)	4(3)	2(1)	1(2)
F(6)	32(3)	42(4)	20(2)	6(2)	3(2)	7(3)
F(1)	35(6)	58(4)	21(5)	-2(3)	-5(4)	13(4)
N(1)	21(1)	24(1)	12(1)	-2(1)	1(1)	-1(1)
C(12)	21(1)	28(1)	13(1)	-3(1)	1(1)	-2(1)
F(3)	56(4)	74(3)	71(6)	33(3)	-15(3)	-16(3)
C(6)	27(1)	22(1)	14(1)	5(1)	0(1)	-1(1)
C(7)	28(1)	28(1)	16(1)	5(1)	1(1)	-4(1)
C(2)	35(1)	25(1)	22(1)	5(1)	1(1)	-8(1)
C(11)	35(1)	28(1)	14(1)	-2(1)	4(1)	-7(1)
C(1)	29(1)	28(1)	20(1)	4(1)	7(1)	-6(1)
C(3)	48(2)	20(1)	23(1)	0(1)	3(1)	-1(1)
C(8)	21(1)	36(1)	25(1)	-2(1)	6(1)	3(1)
C(5)	25(1)	26(1)	31(1)	5(1)	4(1)	1(1)
C(4)	39(1)	27(1)	36(1)	2(1)	13(1)	7(1)
C(10)	56(2)	24(1)	23(1)	0(1)	13(1)	8(1)
C(9)	31(1)	42(2)	28(1)	3(1)	7(1)	15(1)
C(15)	57(2)	46(2)	27(1)	1(1)	8(1)	-29(1)
C(13)	41(1)	40(2)	43(2)	-7(1)	22(1)	-8(1)
B(1)	20(1)	43(1)	20(1)	2(1)	3(1)	3(1)
C(14A)	32(2)	28(3)	44(3)	-5(2)	10(2)	-9(2)
C(14)	41(4)	26(4)	26(3)	-5(3)	8(3)	-11(3)
F(4)	38(2)	40(2)	90(3)	-6(2)	10(2)	2(1)
F(5)	39(2)	75(4)	18(1)	-1(2)	3(1)	0(3)
F(7)	21(1)	51(4)	29(1)	4(3)	2(1)	1(2)
F(2)	26(1)	118(2)	21(1)	-7(1)	6(1)	13(1)

Table S11. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3).

	x	y	z	U(eq)
H(12)	4150	4949	2970	26
H(7A)	1394	4077	4094	30
H(7B)	3231	4047	4027	30
H(2)	-1397	2520	855	35
H(1)	-711	3412	2483	31
H(3)	542	2095	-120	38
H(8A)	-39	5290	3324	33
H(8B)	-544	4758	2081	33
H(5)	3860	3456	2136	34
H(4)	3155	2567	498	40
H(10A)	1575	6462	2950	41
H(10B)	1331	6715	1459	41
H(9A)	-961	6052	1592	41
H(9B)	-55	5615	696	41
H(15C)	4300	6865	2473	53
H(15D)	5023	6240	3524	53
H(15B)	5447	6028	3102	53
H(15A)	4367	6731	3152	53
H(13C)	5539	5894	-94	47
H(13D)	4589	6637	6	47
H(13A)	5808	5819	551	47
H(13B)	4735	6393	-470	47
H(14A)	6256	5712	2231	42
H(14B)	6580	6563	2105	42
H(14C)	4439	7117	1104	38
H(14D)	6248	6823	1733	38

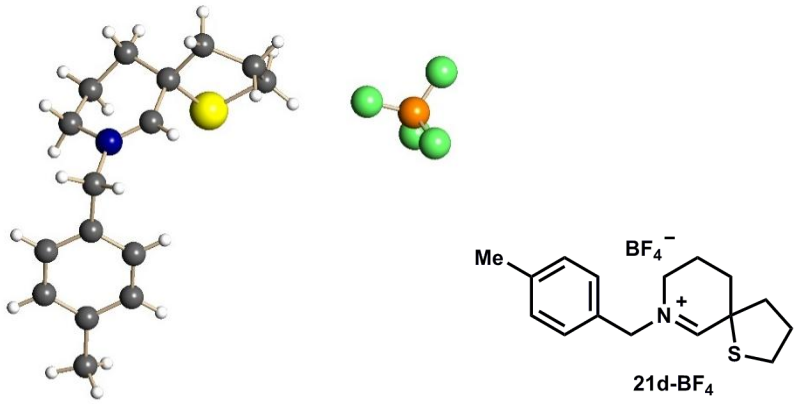


Figure S23. X-ray crystal structure of **21d-BF$_4$**.

Table S12. Crystal data and structure refinement.

Identification code	shenvi38	
Empirical formula	C16 H22 B F4 N S	
Formula weight	347.21	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 8.0327(5) Å	α= 90°.
	b = 18.8756(15) Å	β= 106.392(3)°.
	c = 11.6576(10) Å	γ = 90°.
Volume	1695.7(2) Å^3	
Z	4	
Density (calculated)	1.360 Mg/m^3	
Absorption coefficient	0.227 mm^{-1}	
F(000)	728	
Crystal size	0.29 x 0.26 x 0.05 mm^3	
Theta range for data collection	2.117 to 26.393°.	
Index ranges	-9<=h<=10, -23<=k<=23, -13<=l<=14	
Reflections collected	15607	
Independent reflections	3463 [R(int) = 0.0397]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.1848 and 0.1529	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3463 / 0 / 209	

Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma(I)]	R1 = 0.0678, wR2 = 0.1724
R indices (all data)	R1 = 0.0877, wR2 = 0.1886
Extinction coefficient	n/a
Largest diff. peak and hole	0.747 and -0.632 e.$Å^{-3}$

Table S13. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	4626(1)	3188(1)	8441(1)	32(1)
F(1)	-1477(3)	1066(2)	5947(3)	80(1)
F(2)	-1335(4)	1925(1)	7283(3)	85(1)
F(3)	188(4)	2006(1)	5918(3)	77(1)
F(4)	898(4)	1214(3)	7359(3)	130(2)
N(1)	656(3)	3661(1)	8784(2)	24(1)
C(1)	4604(4)	1939(2)	9498(3)	38(1)
C(2)	4174(4)	2473(2)	10345(3)	37(1)
C(3)	3563(4)	3169(2)	9665(3)	28(1)
C(4)	1695(4)	3131(2)	8967(2)	26(1)
C(5)	-1181(4)	3590(2)	8082(3)	28(1)
C(6)	-1531(3)	3964(1)	6893(3)	25(1)
C(7)	-932(4)	3675(2)	5987(3)	29(1)
C(8)	-1255(4)	4008(2)	4891(3)	34(1)
C(9)	-2171(4)	4639(2)	4668(3)	36(1)
C(10)	-2551(5)	4983(2)	3451(3)	51(1)
C(11)	5683(5)	2330(2)	8835(3)	40(1)
C(12)	-2729(4)	4936(2)	5583(3)	39(1)
C(13)	-2417(4)	4603(2)	6687(3)	34(1)
C(14)	1160(4)	4371(2)	9312(3)	28(1)
C(15)	3097(4)	4469(2)	9747(3)	32(1)
C(16)	3963(4)	3824(2)	10449(3)	33(1)
B(1)	-436(5)	1561(2)	6633(3)	31(1)

Table S14. Bond lengths [Å] and angles [°].

S(1)-C(3)	1.858(3)	C(6)-C(13)	1.387(4)
S(1)-C(11)	1.825(3)	C(7)-H(7)	0.9500
F(1)-B(1)	1.354(4)	C(7)-C(8)	1.382(4)
F(2)-B(1)	1.370(4)	C(8)-H(8)	0.9500
F(3)-B(1)	1.373(4)	C(8)-C(9)	1.385(5)
F(4)-B(1)	1.335(5)	C(9)-C(10)	1.511(5)
N(1)-C(4)	1.281(4)	C(9)-C(12)	1.386(5)
N(1)-C(5)	1.477(4)	C(10)-H(10A)	0.9800
N(1)-C(14)	1.483(3)	C(10)-H(10B)	0.9800
C(1)-H(1A)	0.9900	C(10)-H(10C)	0.9800
C(1)-H(1B)	0.9900	C(11)-H(11A)	0.9900
C(1)-C(2)	1.518(5)	C(11)-H(11B)	0.9900
C(1)-C(11)	1.507(5)	C(12)-H(12)	0.9500
C(2)-H(2A)	0.9900	C(12)-C(13)	1.390(5)
C(2)-H(2B)	0.9900	C(13)-H(13)	0.9500
C(2)-C(3)	1.541(4)	C(14)-H(14A)	0.9900
C(3)-C(4)	1.493(4)	C(14)-H(14B)	0.9900
C(3)-C(16)	1.516(4)	C(14)-C(15)	1.506(4)
C(4)-H(4)	0.9500	C(15)-H(15A)	0.9900
C(5)-H(5A)	0.9900	C(15)-H(15B)	0.9900
C(5)-H(5B)	0.9900	C(15)-C(16)	1.522(4)
C(5)-C(6)	1.509(4)	C(16)-H(16A)	0.9900
C(6)-C(7)	1.390(4)	C(16)-H(16B)	0.9900

C(11)-S(1)-C(3)	94.17(15)	C(11)-C(1)-H(1B)	110.5
C(4)-N(1)-C(5)	121.6(2)	C(11)-C(1)-C(2)	106.1(3)
C(4)-N(1)-C(14)	123.2(2)	C(1)-C(2)-H(2A)	109.8
C(5)-N(1)-C(14)	115.1(2)	C(1)-C(2)-H(2B)	109.8
H(1A)-C(1)-H(1B)	108.7	C(1)-C(2)-C(3)	109.3(2)
C(2)-C(1)-H(1A)	110.5	H(2A)-C(2)-H(2B)	108.3
C(2)-C(1)-H(1B)	110.5	C(3)-C(2)-H(2A)	109.8
C(11)-C(1)-H(1A)	110.5	C(3)-C(2)-H(2B)	109.8

C(2)-C(3)-S(1)	105.2(2)	C(1)-C(11)-H(11A)	110.6
C(4)-C(3)-S(1)	101.00(18)	C(1)-C(11)-H(11B)	110.6
C(4)-C(3)-C(2)	111.4(3)	H(11A)-C(11)-H(11B)	108.8
C(4)-C(3)-C(16)	112.2(2)	C(9)-C(12)-H(12)	119.4
C(16)-C(3)-S(1)	112.5(2)	C(9)-C(12)-C(13)	121.2(3)
C(16)-C(3)-C(2)	113.7(2)	C(13)-C(12)-H(12)	119.4
N(1)-C(4)-C(3)	124.1(3)	C(6)-C(13)-C(12)	120.2(3)
N(1)-C(4)-H(4)	117.9	C(6)-C(13)-H(13)	119.9
C(3)-C(4)-H(4)	117.9	C(12)-C(13)-H(13)	119.9
N(1)-C(5)-H(5A)	109.4	N(1)-C(14)-H(14A)	109.1
N(1)-C(5)-H(5B)	109.4	N(1)-C(14)-H(14B)	109.1
N(1)-C(5)-C(6)	111.4(2)	N(1)-C(14)-C(15)	112.7(2)
H(5A)-C(5)-H(5B)	108.0	H(14A)-C(14)-H(14B)	107.8
C(6)-C(5)-H(5A)	109.4	C(15)-C(14)-H(14A)	109.1
C(6)-C(5)-H(5B)	109.4	C(15)-C(14)-H(14B)	109.1
C(7)-C(6)-C(5)	120.0(3)	C(14)-C(15)-H(15A)	109.5
C(13)-C(6)-C(5)	121.3(3)	C(14)-C(15)-H(15B)	109.5
C(13)-C(6)-C(7)	118.8(3)	C(14)-C(15)-C(16)	110.8(3)
C(6)-C(7)-H(7)	119.7	H(15A)-C(15)-H(15B)	108.1
C(8)-C(7)-C(6)	120.6(3)	C(16)-C(15)-H(15A)	109.5
C(8)-C(7)-H(7)	119.7	C(16)-C(15)-H(15B)	109.5
C(7)-C(8)-H(8)	119.5	C(3)-C(16)-C(15)	109.9(2)
C(7)-C(8)-C(9)	121.1(3)	C(3)-C(16)-H(16A)	109.7
C(9)-C(8)-H(8)	119.5	C(3)-C(16)-H(16B)	109.7
C(8)-C(9)-C(10)	120.1(3)	C(15)-C(16)-H(16A)	109.7
C(8)-C(9)-C(12)	118.2(3)	C(15)-C(16)-H(16B)	109.7
C(12)-C(9)-C(10)	121.7(3)	H(16A)-C(16)-H(16B)	108.2
C(9)-C(10)-H(10A)	109.5	F(1)-B(1)-F(2)	109.7(3)
C(9)-C(10)-H(10B)	109.5	F(1)-B(1)-F(3)	109.5(3)
C(9)-C(10)-H(10C)	109.5	F(2)-B(1)-F(3)	111.6(3)
H(10A)-C(10)-H(10B)	109.5	F(4)-B(1)-F(1)	106.7(4)
H(10A)-C(10)-H(10C)	109.5	F(4)-B(1)-F(2)	110.4(3)
H(10B)-C(10)-H(10C)	109.5	F(4)-B(1)-F(3)	108.7(3)
S(1)-C(11)-H(11A)	110.6		
S(1)-C(11)-H(11B)	110.6		
C(1)-C(11)-S(1)	105.6(2)		

Table S15. Anisotropic displacement parameters ($Å^2 x\ 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	36(1)	35(1)	27(1)	6(1)	11(1)	6(1)
F(1)	71(2)	89(2)	90(2)	-56(2)	39(2)	-37(1)
F(2)	159(3)	32(1)	105(2)	-16(1)	104(2)	-11(1)
F(3)	141(3)	28(1)	94(2)	1(1)	88(2)	2(1)
F(4)	64(2)	210(4)	97(2)	82(3)	-9(2)	21(2)
N(1)	28(1)	20(1)	25(1)	0(1)	8(1)	-2(1)
C(1)	38(2)	29(2)	45(2)	6(1)	8(2)	5(1)
C(2)	46(2)	37(2)	26(2)	10(1)	7(1)	8(1)
C(3)	32(2)	31(2)	24(1)	5(1)	9(1)	4(1)
C(4)	34(2)	22(1)	24(1)	1(1)	12(1)	-1(1)
C(5)	24(1)	26(1)	33(2)	1(1)	10(1)	-4(1)
C(6)	24(1)	22(1)	28(1)	0(1)	4(1)	-4(1)
C(7)	32(2)	22(1)	34(2)	-2(1)	9(1)	-2(1)
C(8)	35(2)	38(2)	31(2)	-4(1)	9(1)	-9(1)
C(9)	32(2)	35(2)	35(2)	7(1)	2(1)	-13(1)
C(10)	52(2)	55(2)	39(2)	16(2)	0(2)	-16(2)
C(11)	44(2)	38(2)	38(2)	6(1)	13(2)	15(2)
C(12)	38(2)	26(2)	47(2)	7(1)	2(1)	3(1)
C(13)	35(2)	30(2)	39(2)	-2(1)	10(1)	3(1)
C(14)	35(2)	19(1)	31(2)	-2(1)	9(1)	-1(1)
C(15)	34(2)	27(2)	34(2)	-5(1)	7(1)	-4(1)
C(16)	32(2)	39(2)	26(2)	-1(1)	5(1)	-1(1)
B(1)	44(2)	21(2)	28(2)	-1(1)	8(1)	-3(1)

Table S16. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3).

	x	y	z	U(eq)
H(1A)	5263	1536	9950	46
H(1B)	3528	1755	8932	46
H(2A)	5213	2563	11024	44
H(2B)	3248	2283	10667	44
H(4)	1250	2687	8637	31
H(5A)	-1933	3793	8541	33
H(5B)	-1474	3082	7945	33
H(7)	-294	3244	6123	35
H(8)	-844	3801	4280	41
H(10A)	-1476	5020	3215	77
H(10B)	-3030	5458	3484	77
H(10C)	-3394	4695	2864	77
H(11A)	5716	2067	8107	48
H(11B)	6886	2393	9350	48
H(12)	-3335	5374	5453	47
H(13)	-2812	4814	7303	41
H(14A)	662	4440	9990	34
H(14B)	661	4737	8704	34
H(15A)	3369	4894	10264	39
H(15B)	3561	4544	9055	39
H(16A)	5234	3897	10728	39
H(16B)	3536	3757	11159	39

6. EC_{50} and time course cell viability experiments

HT29 and Jurkat cells were maintained in optimal media as suggested by ATCC. 14 h prior to addition of nuphar derivatives, cells were plated into 96-well tissue culture-treated plates (50 µL total volume) at a density of 5,000 cells per well.

Cell viability EC_{50} experiments were performed in a final volume of 50 µL with 0.05 – 50 µM nuphar compounds or 12 nM – 50 µM compound 3a (0.5% DMSO). 1 µM staurosporine (Trevigen) and 0.5% DMSO were used as the positive and negative controls, respectively. The cells were incubated at 37 °C in the presence of 5% CO_2 and assessed for viability by the addition of 50 µL of CellTiter-Glo® (Promega) at 48 h incubation. After a 10-min incubation at room temperature, luminescence was measured on a PerkinElmer EnVision plate reader. All assay data was collected in triplicate with EC_{50} values determined using GraphPad Prism.

Rates of HT29 and Jurkat cell death were determined with 1, 5, and 10 µM of compounds 3a, 27,29-31 and 26 or 25 µM compound 13,22 and 23 (0.5% DMSO) and assessed for cellular viability by the addition of 50 µL of CellTiter-Glo® (Promega) at 0, 1, 2, 4, 12, and 24 h post incubation, as described for the cell viability experiments.

7. ABPP Methods

Protein labeling and click chemistry. Jurkat cells were lysed by sonication and diluted to a concentration of 2 mg protein/mL in PBS. Protein concentrations were measured with the Bio-Rad DC™ protein assay reagents A and B (5000113, 5000114; Bio-Rad). 500 µL of proteome sample was treated with 50 µM warhead 26, monomer 13, monomer 22, or monomer 23 (2.5 µL of a 10 mM DMSO stock). Warhead/monomer control samples were treated with 2.5 µL of DMSO. For dimer 27, 500µL of proteome sample was treated with 25 µM compound (1.25 µL of a 10 mM DMSO stock), and the control sample was treated with 1.25 µL of DMSO. Compounds were allowed to react with cell lysate for 1 h at room temperature on a rotator.

Cell lysates were then labeled with 100 µM of IA-alkyne probe using 10 µL of a 10 mM DMSO stock. The labeling reactions were incubated at room temperature for 1 h upon which time the samples were conjugated to isotopically-labeled TEV-cleavable tags (TEV tags) by copper-catalyzed azide-alkyne cycloaddition (CuACC or 'click chemistry'). 60 µL of heavy click chemistry reaction mixture was added to the DMSO-treated control sample and 60 µL of the light reaction mixture was added to the compound-treated sample. The click reaction mixture comprised TEV tags (10 µL of a 5 mM stock, light (fragment treated) or heavy (DMSO treated)), $CuSO_4$ (10 µL of a 50 mM stock in water), and TBTA (30 µL of a 1.7 mM stock in 4:1 tBuOH:DMSO). To this was added TCEP (10 µL of a 50 mM stock). The reaction was performed for 1 h at room temperature.

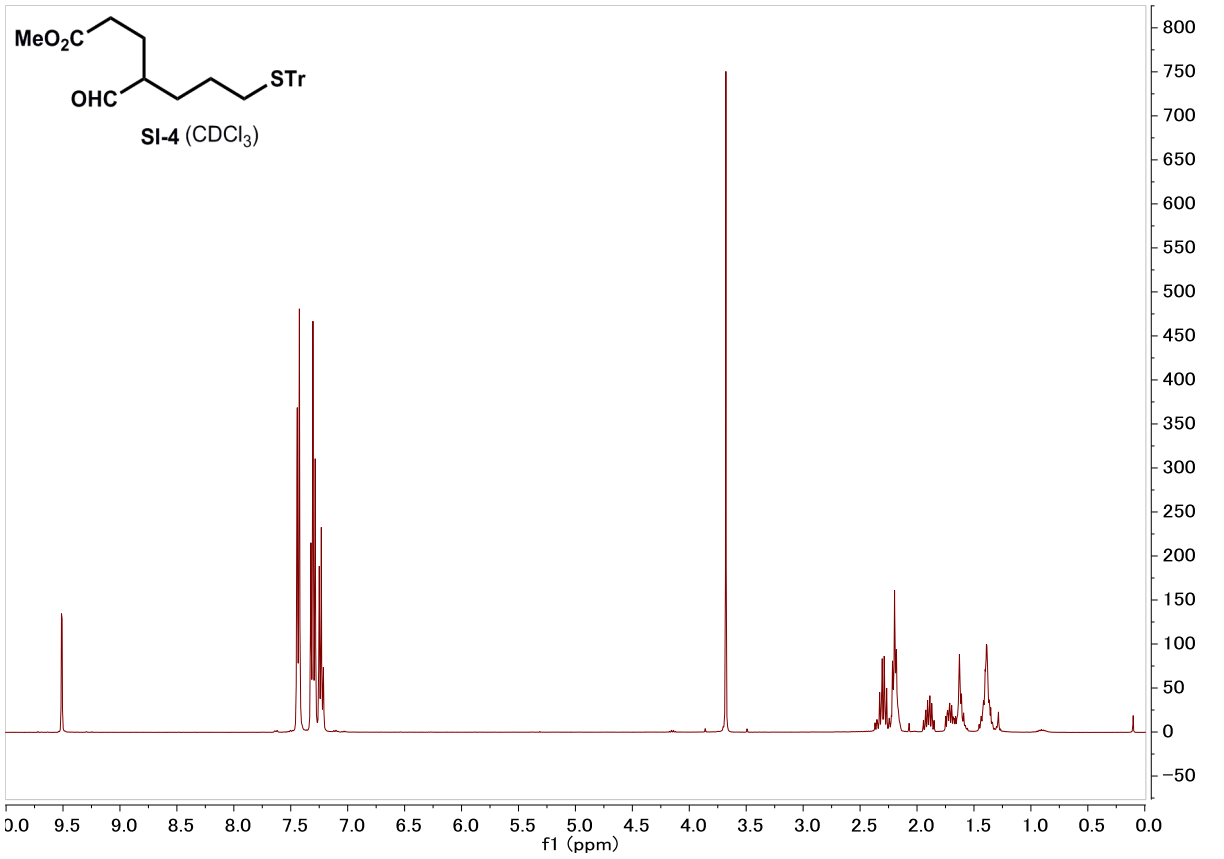
The light- and heavy-labeled samples were then centrifuged (16,000*g*, 5 min, 4 ^{o}C) to harvest the precipitated proteins. The resulting pellets were resuspended in 500 µL of cold methanol by sonication and the heavy and light samples combined pairwise. Combined pellets were then washed with cold MeOH, after which the pellet was solubilized in PBS containing 1.2% SDS by sonication. The samples were heated at 90 ^{o}C for 5 min and subjected to streptavidin enrichment of probe-labeled proteins, sequential on-bead trypsin and TEV digestion, and liquid

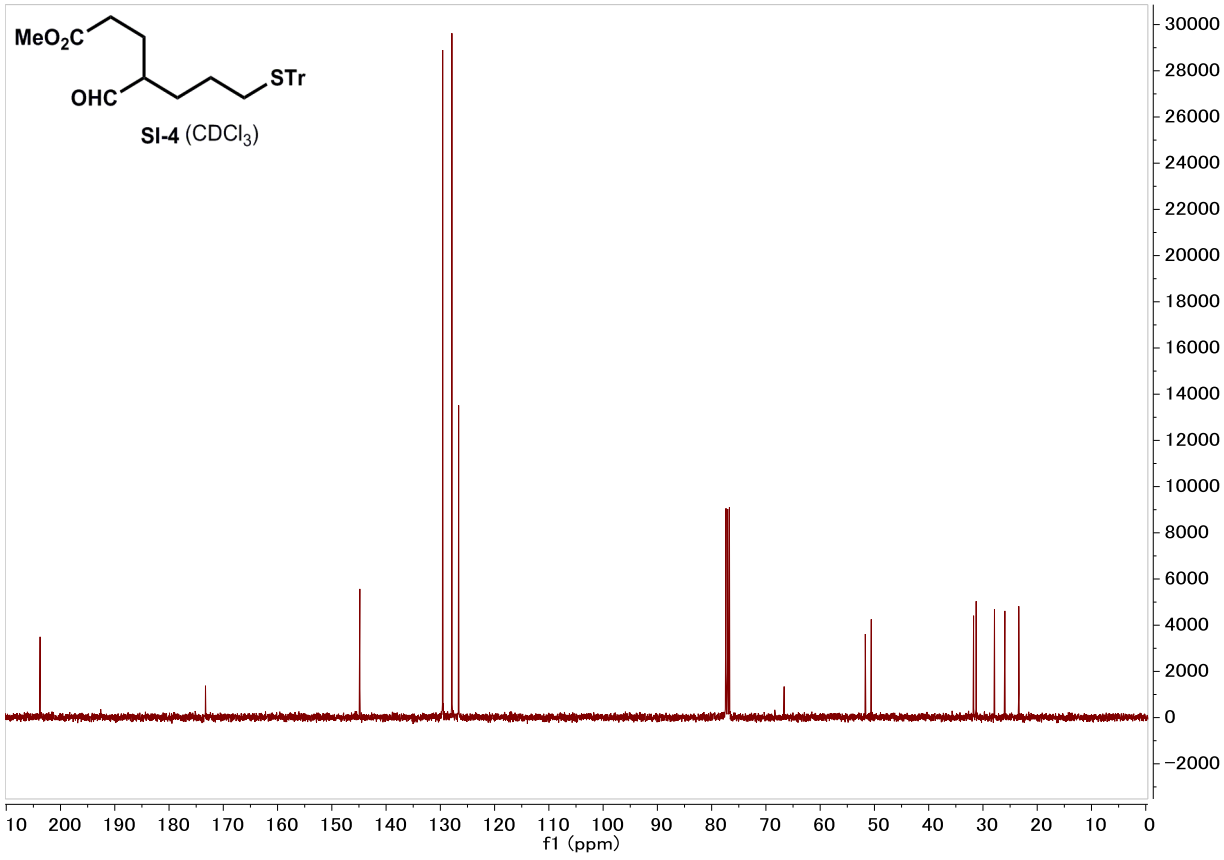
chromatography-tandem mass spectrometry (LC-MS/MS) according to the published isoTOP-ABPP protocols (*1-3*).

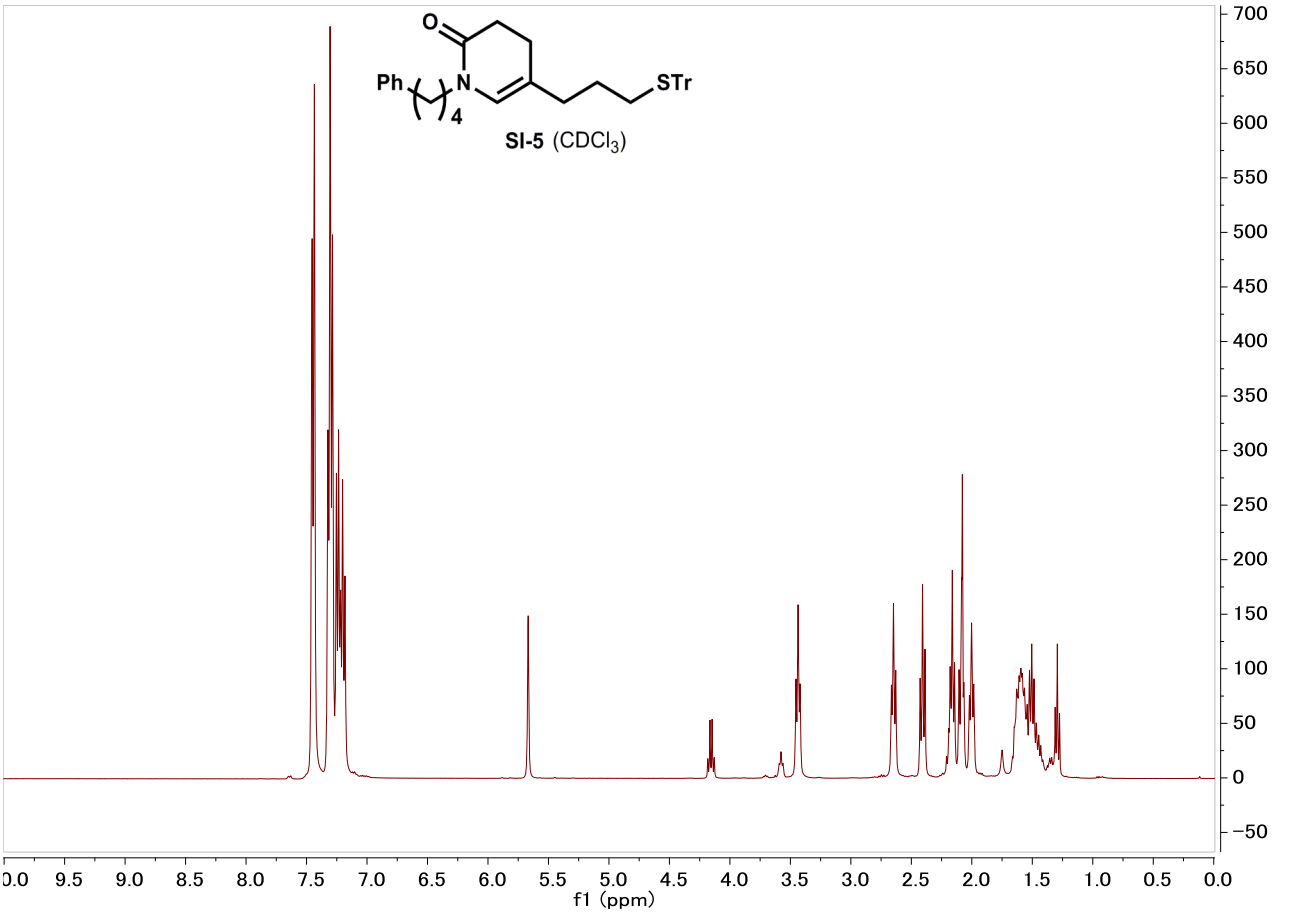
Peptide and protein identification. RAW Xtractor (version 1.9.9.2; available at http://fields.scripps.edu/downloads.php) was used to extract the MS2 spectra data from the raw files. MS2 data were searched against a reverse concatenated, nonredundant variant of the Human UniProt database (release-2012_11) using the ProLuCID algorithm (publicly available at http://fields.scripps.edu/downloads.php) (*4*). Cysteine residues were searched with a static modification for carboxyamidomethylation (+57.02146) and up to one differential modification for either the light or heavy TEV tags (+464.28595 or +470.29976, respectively). Peptides were required to have at least one tryptic terminus and to contain the TEV modification. ProLuCID data was filtered through DTASelect (version 2.0) to achieve a peptide false-positive rate below 1% (*5*).

***R* value calculation and processing.** The quantification of heavy/light ratios (isoTOP-ABPP ratios, *R* values) was performed by in-house CIMAGE software (*3*) using default parameters (3 MS1's per peak and signal to noise threshold of 2.5). Site-specific engagement of electrophilic compounds was assessed by blockade of IA-alkyne probe labeling. For peptides that showed a ≥95% reduction in MS1 peak area from the compound-treated proteome (light TEV tag) when compared to the DMSO treated proteome (heavy TEV tag), a maximal ratio of 20 was assigned. Overlapping peptides with the same labeled cysteine (for example, same local sequence around the labeled cysteines but different charge states, MudPIT segment numbers, or tryptic termini) were grouped together, and the median ratio from each group was recorded as the *R* value of the peptide for that run.

8. NMR Spectra



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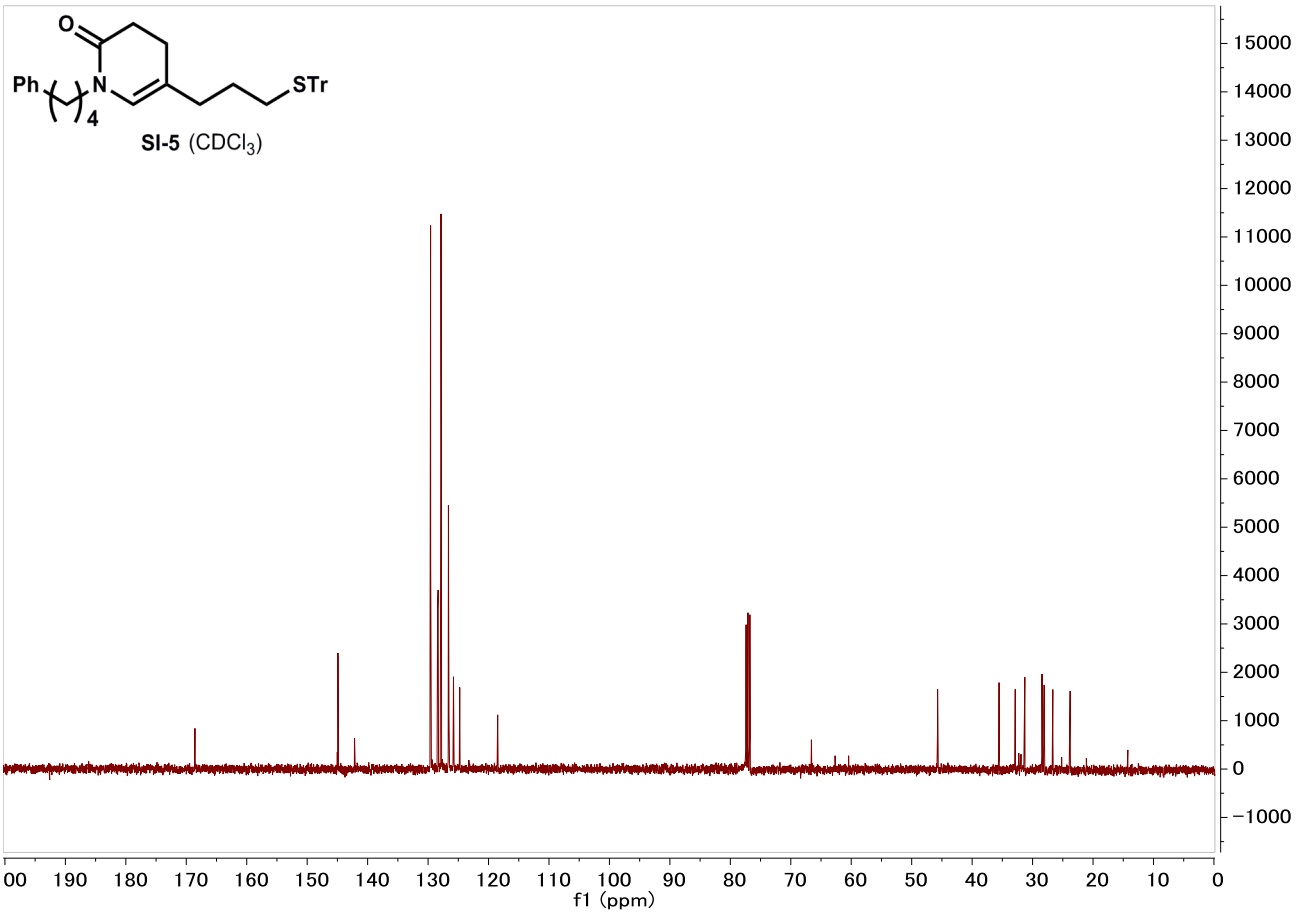
450
400
350
300
250
200
150
100
50
0
−50
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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0
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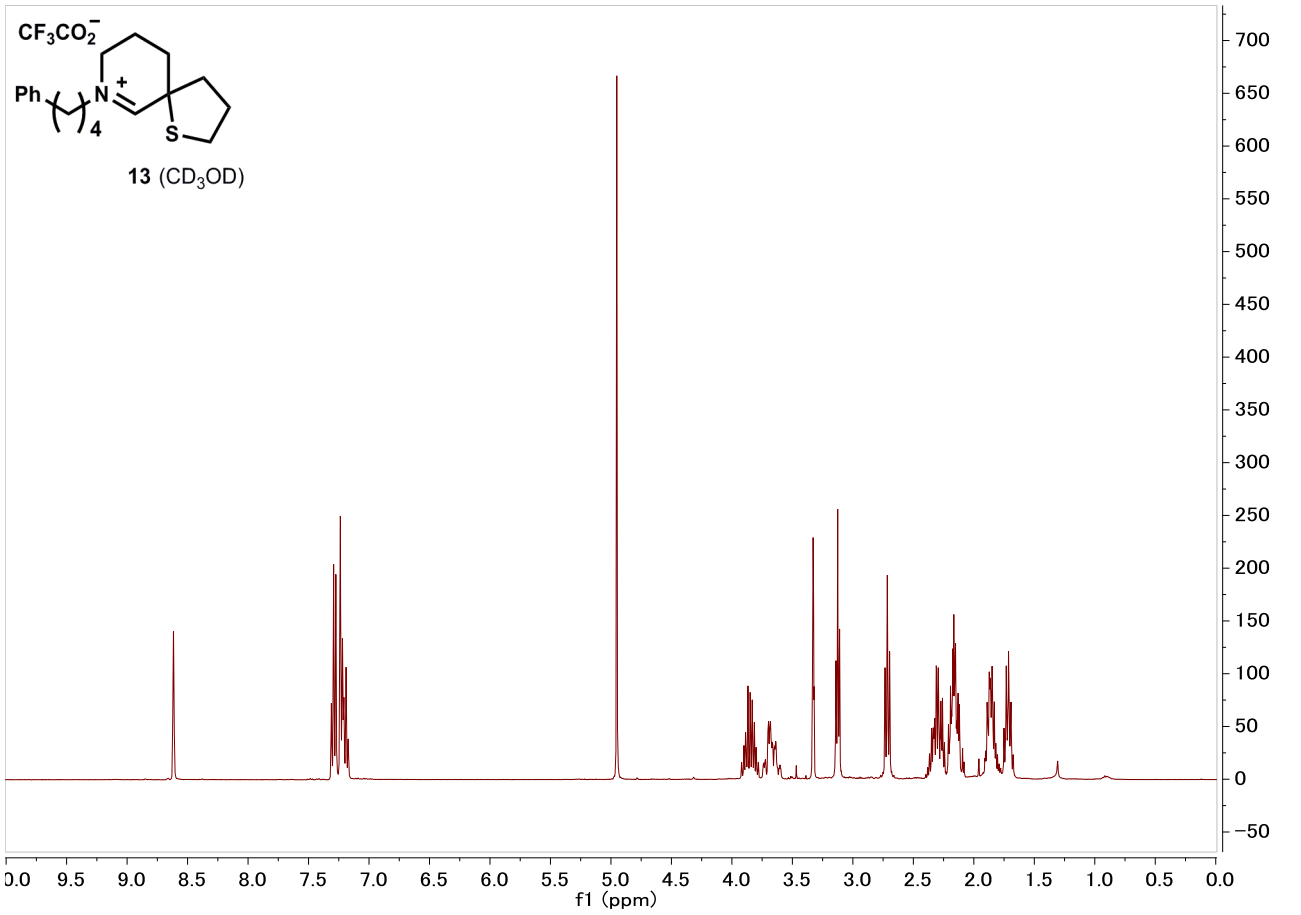
f1 (ppm)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550
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400
350
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250
200
150
100
50
0
−50
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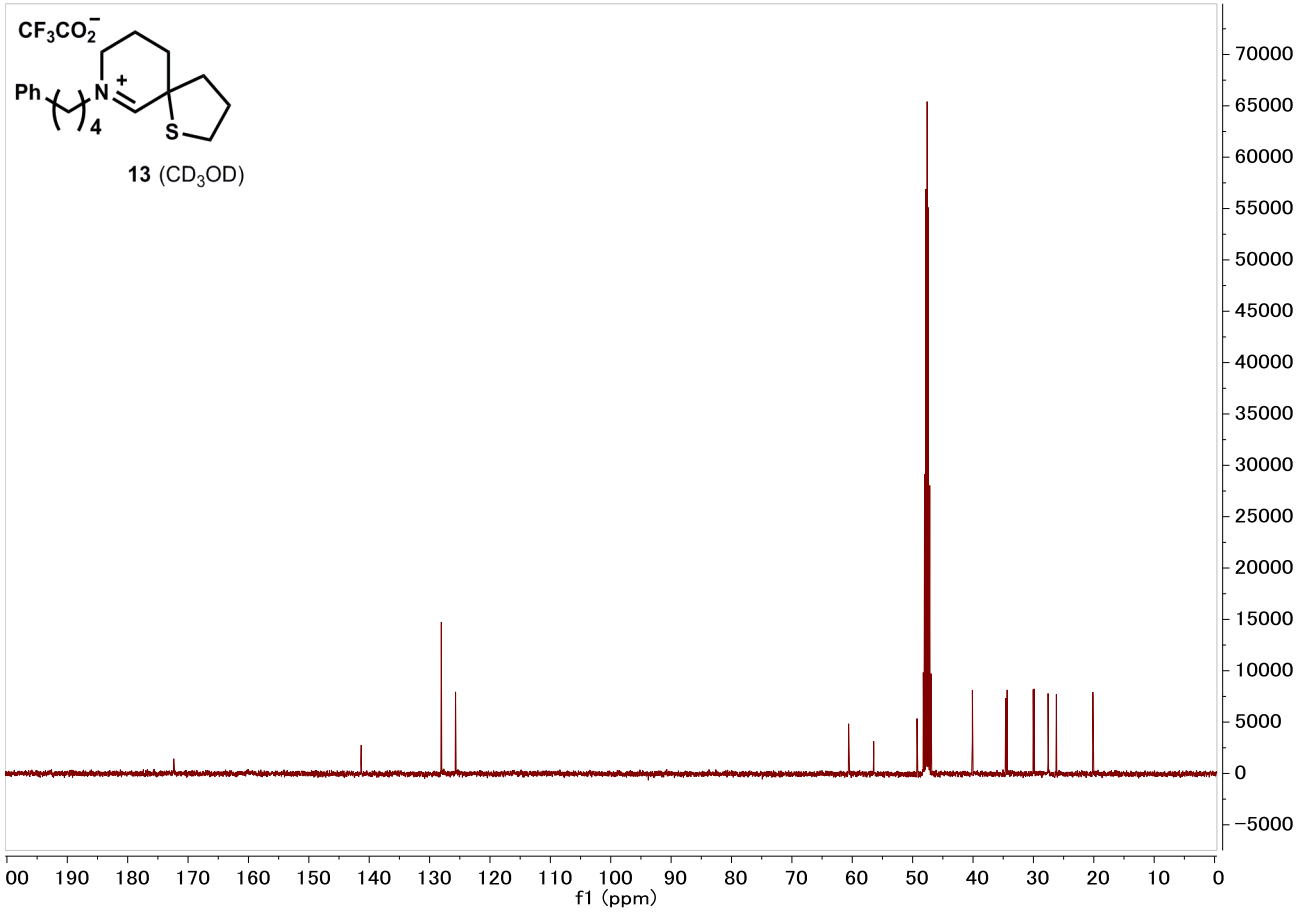
f1 (ppm)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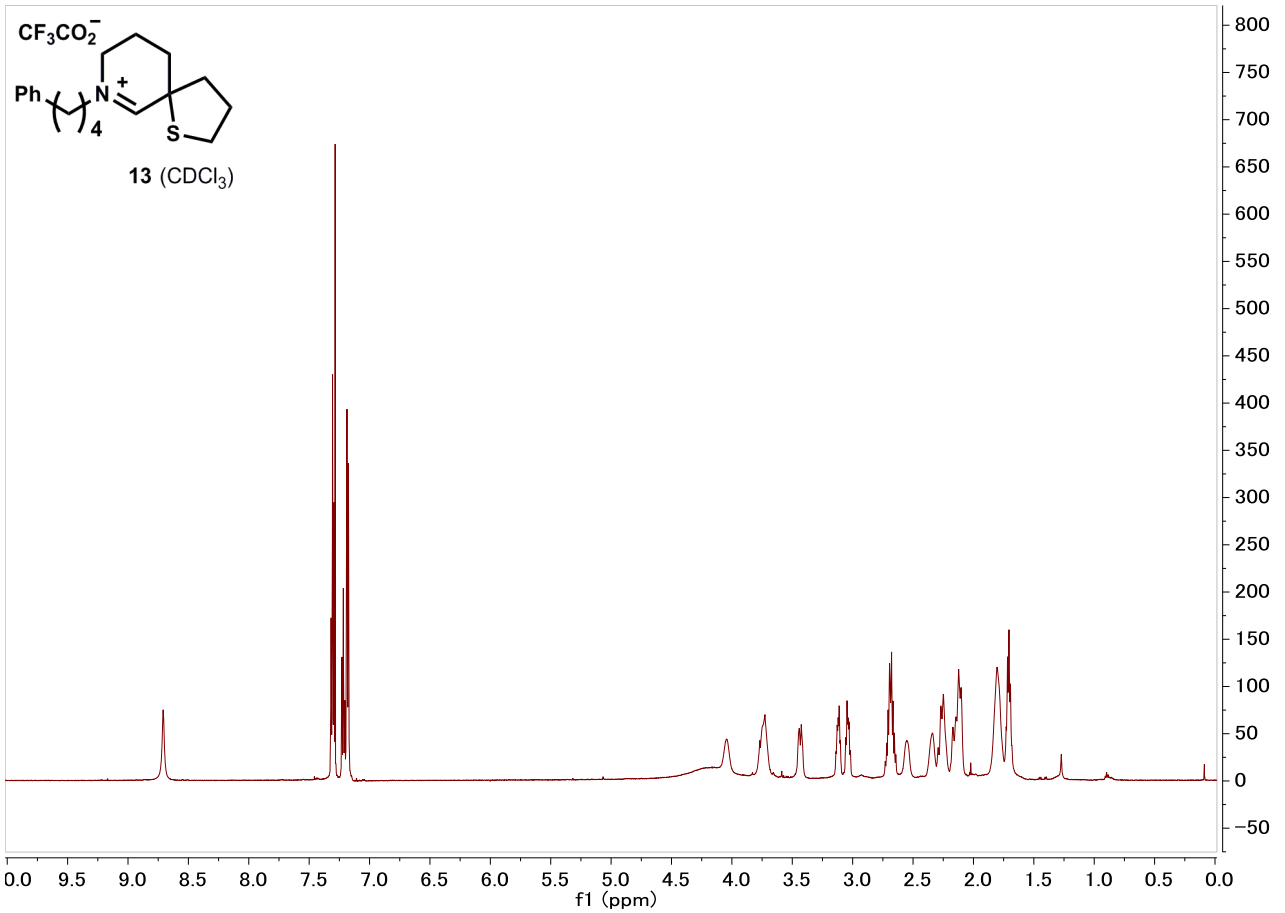
f1 (ppm)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4
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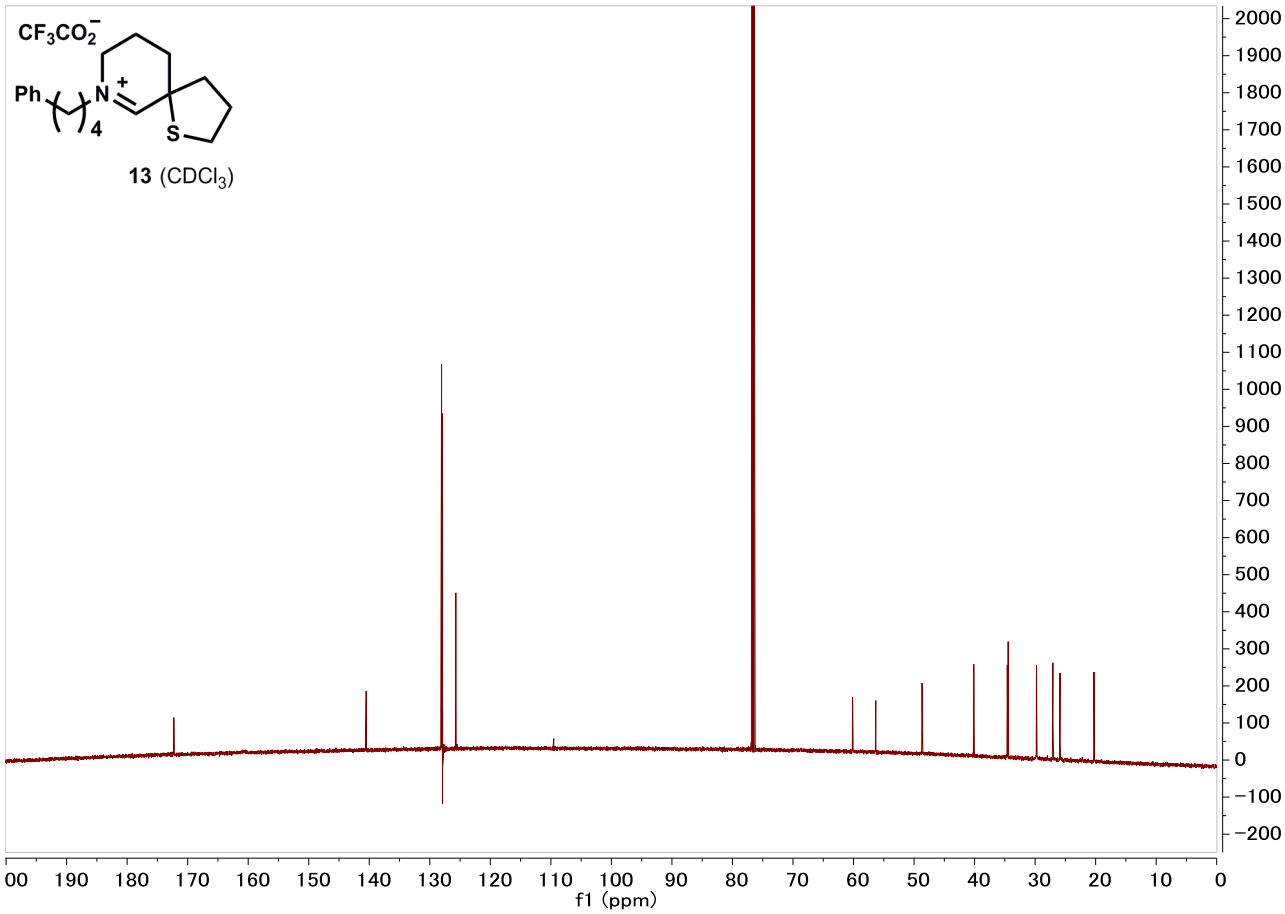
f1 (ppm)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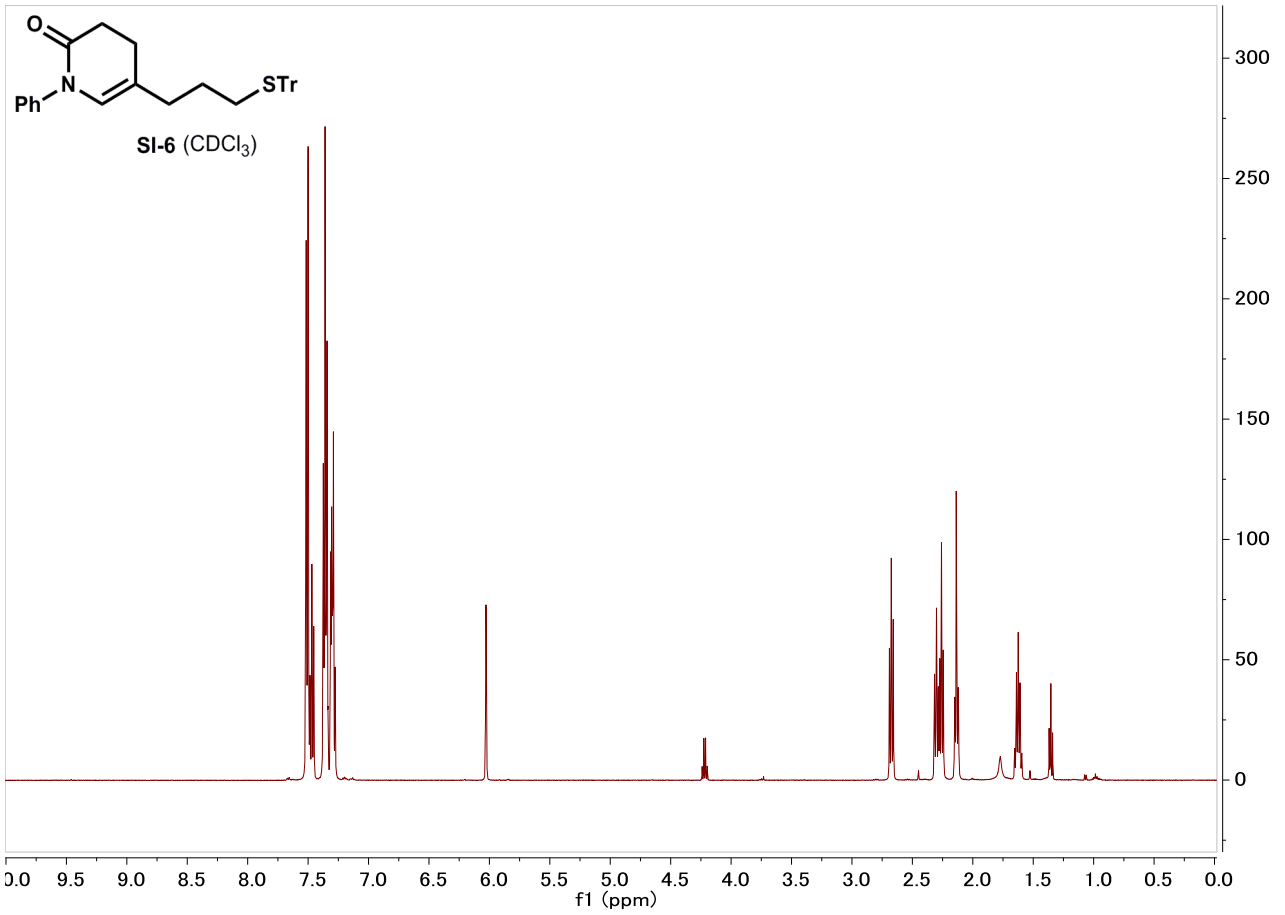
Ph
N+
4
S
13 (CDCl3)
f1 (ppm)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Ph
STr
SI-6 (CDCl3)
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50
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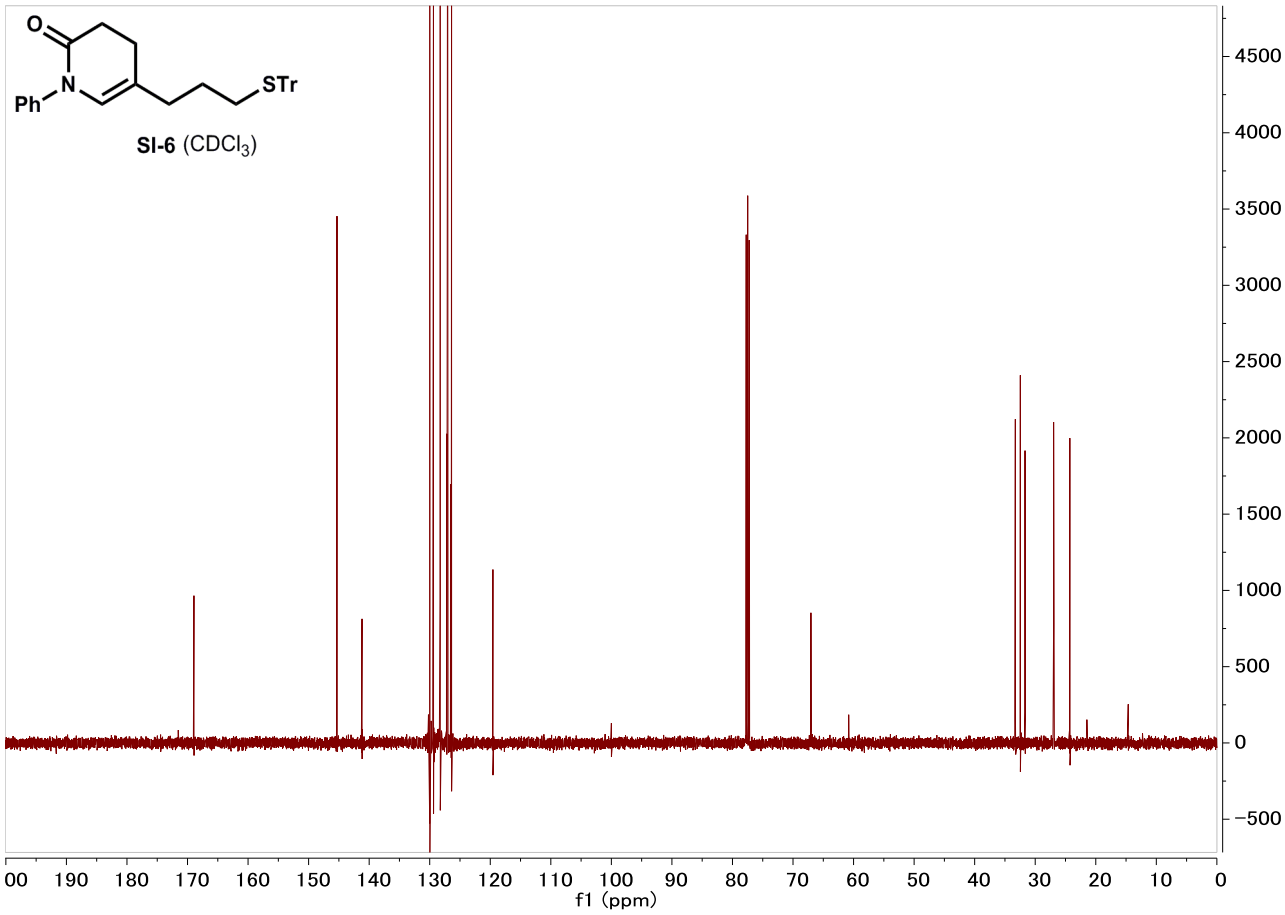
f1 (ppm)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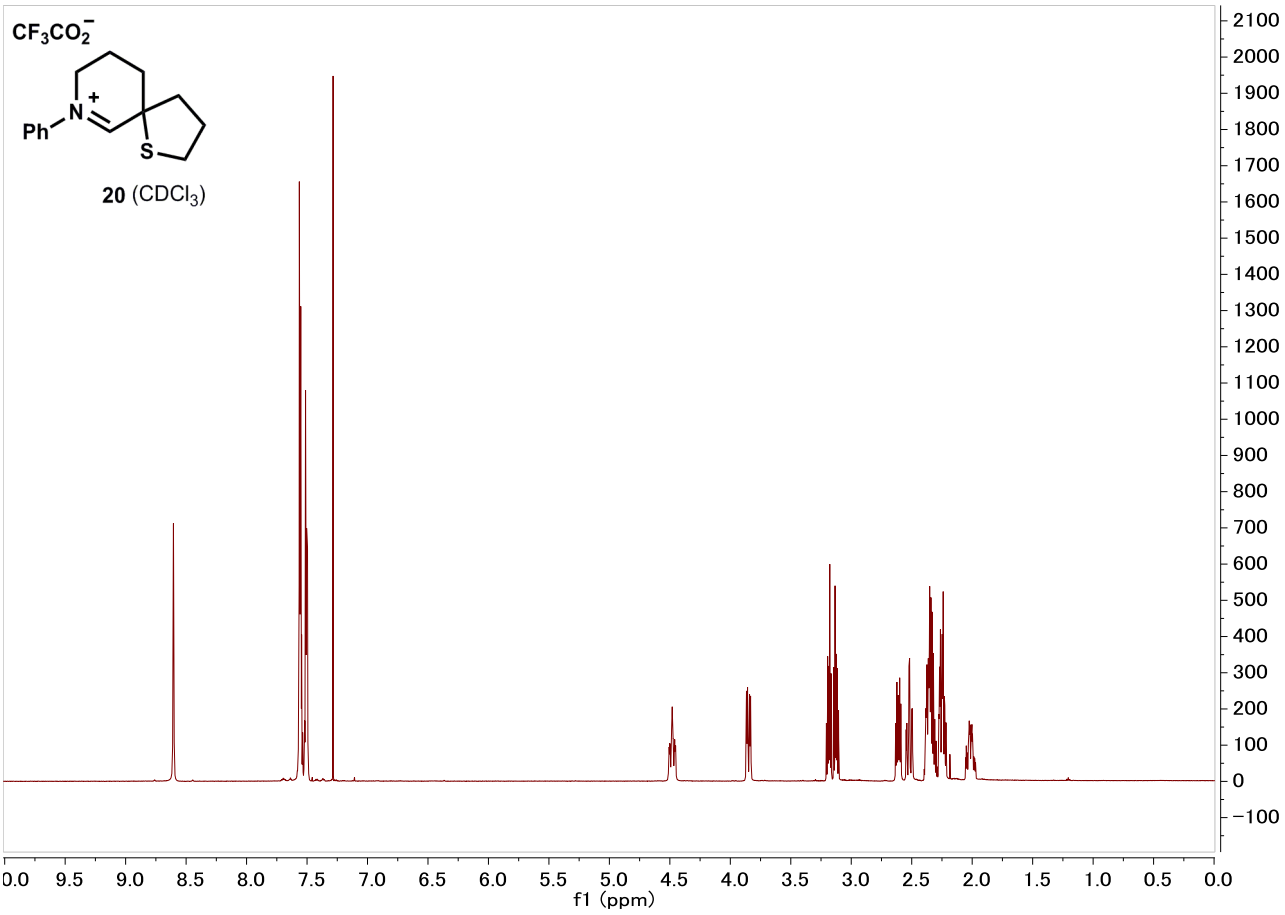
f1 (ppm)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S
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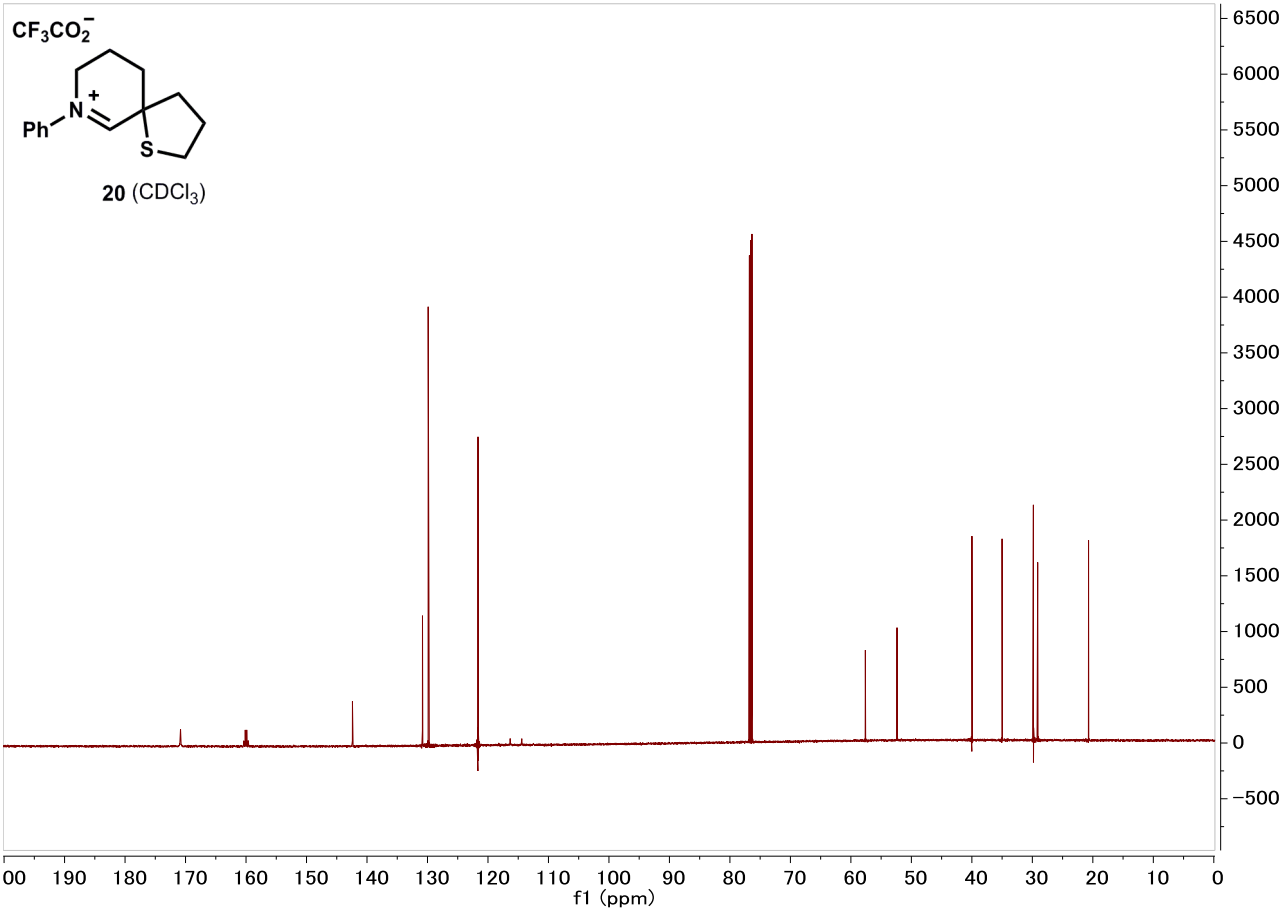
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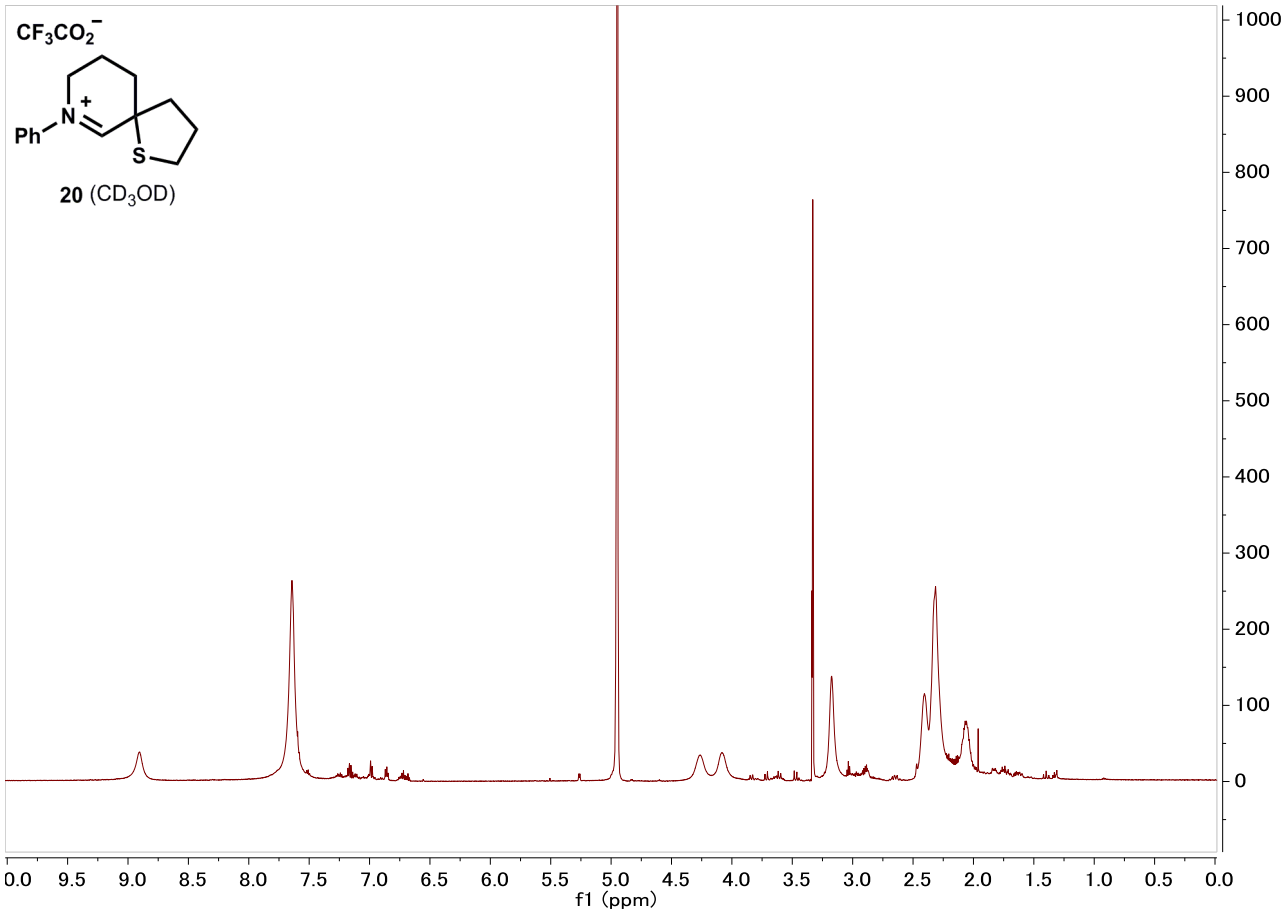
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N+
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600
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300
200
100
0
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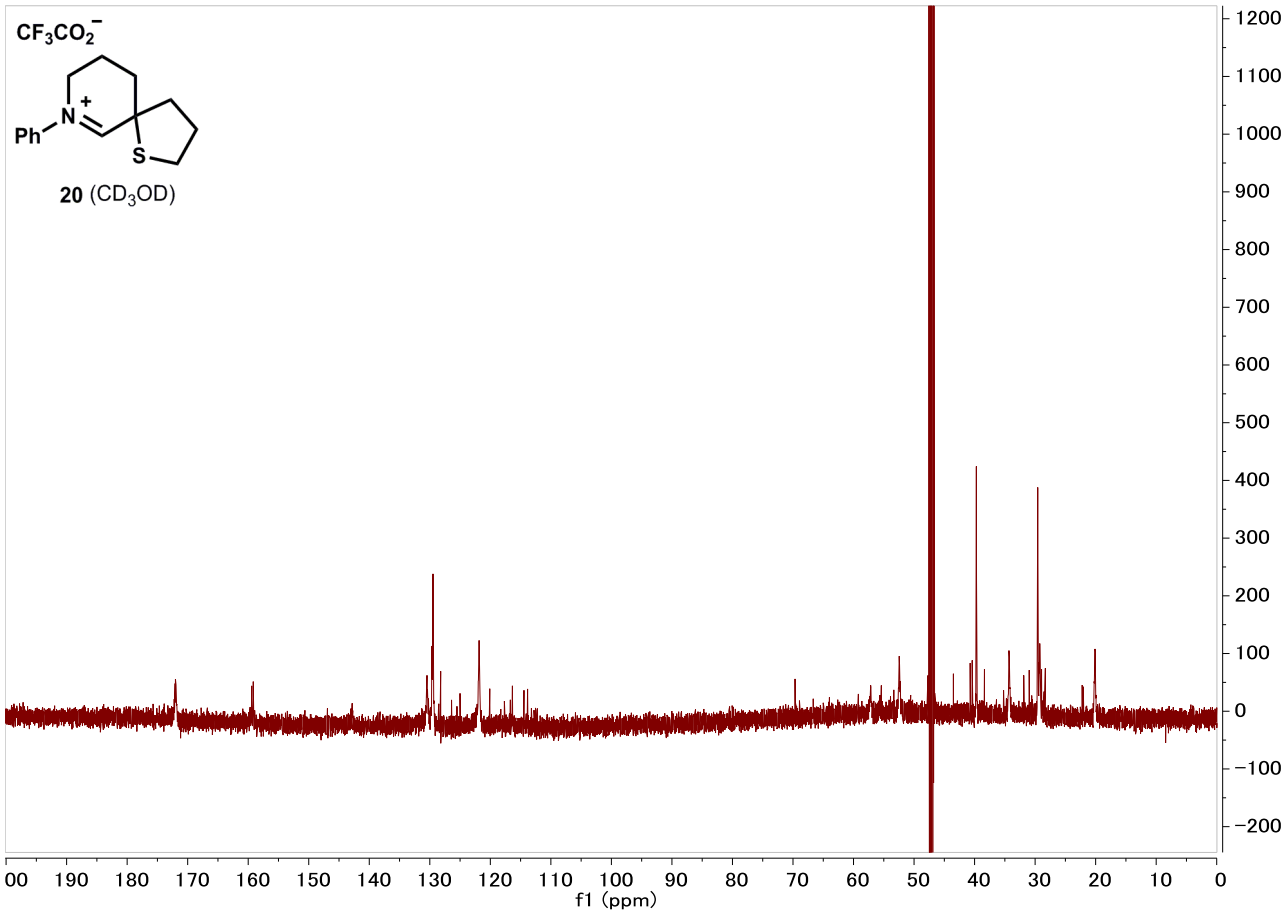
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N+
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800
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500
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100
0
−100
−200
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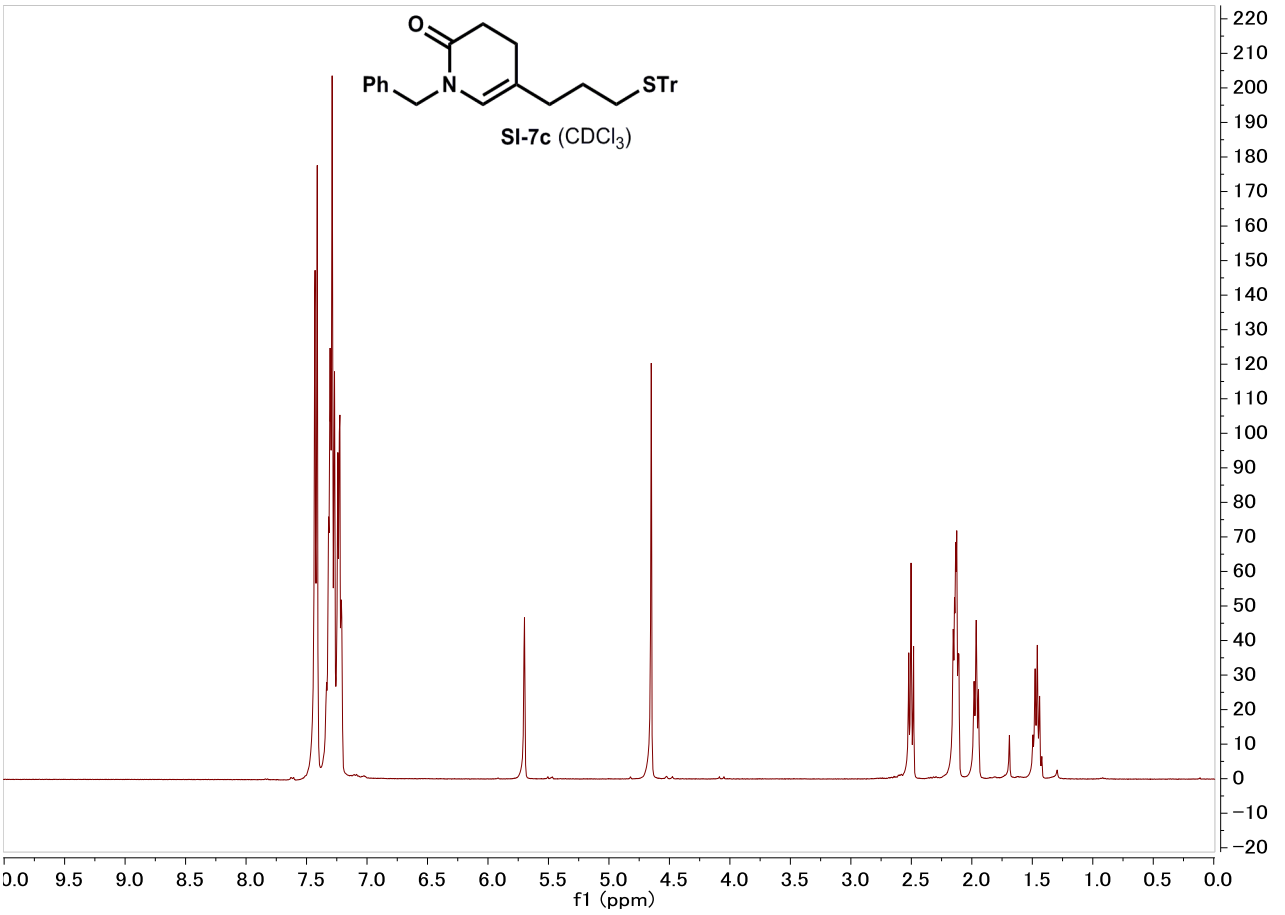
f1 (ppm)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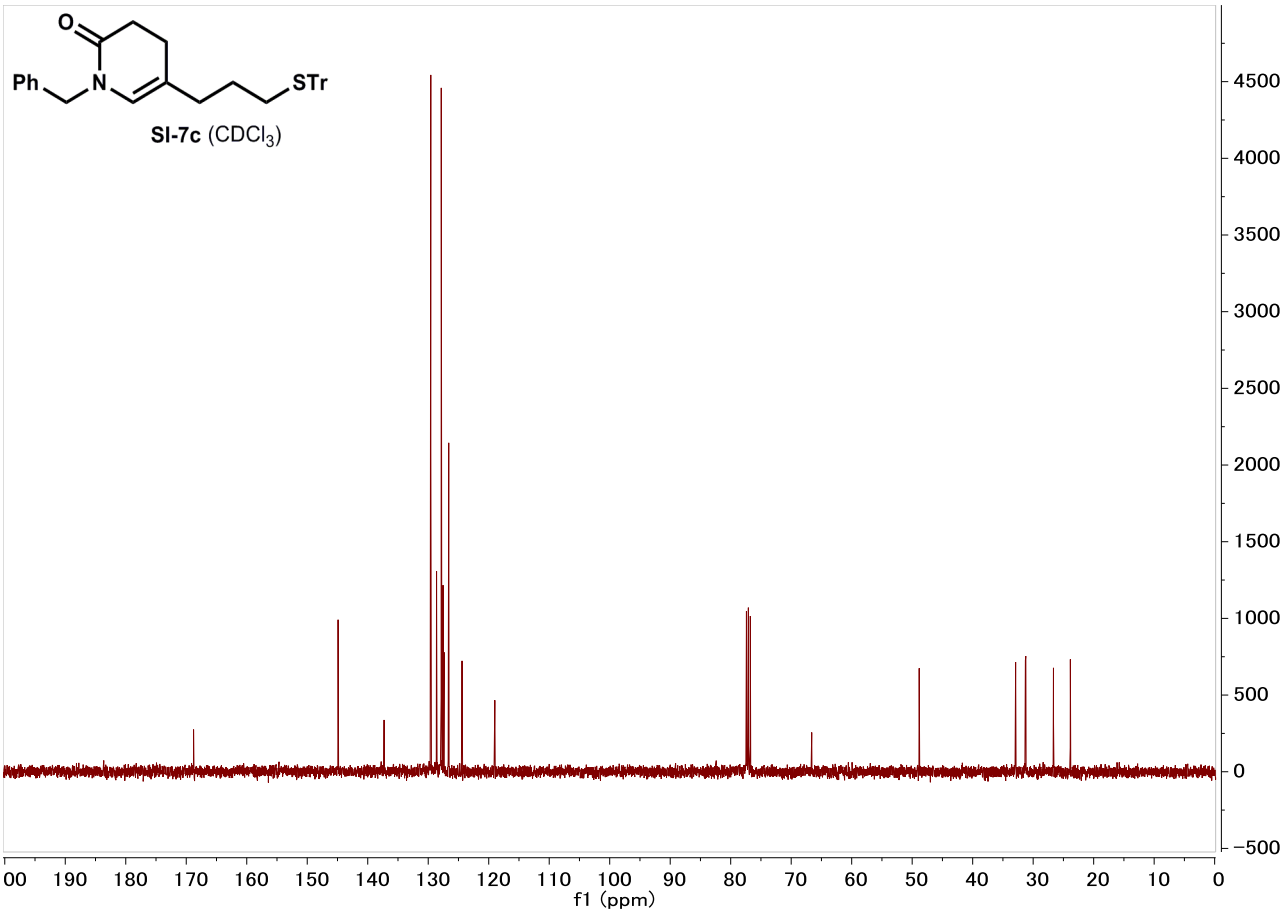
Ph
N
STr
SI-7c (CDCl3)
f1 (ppm)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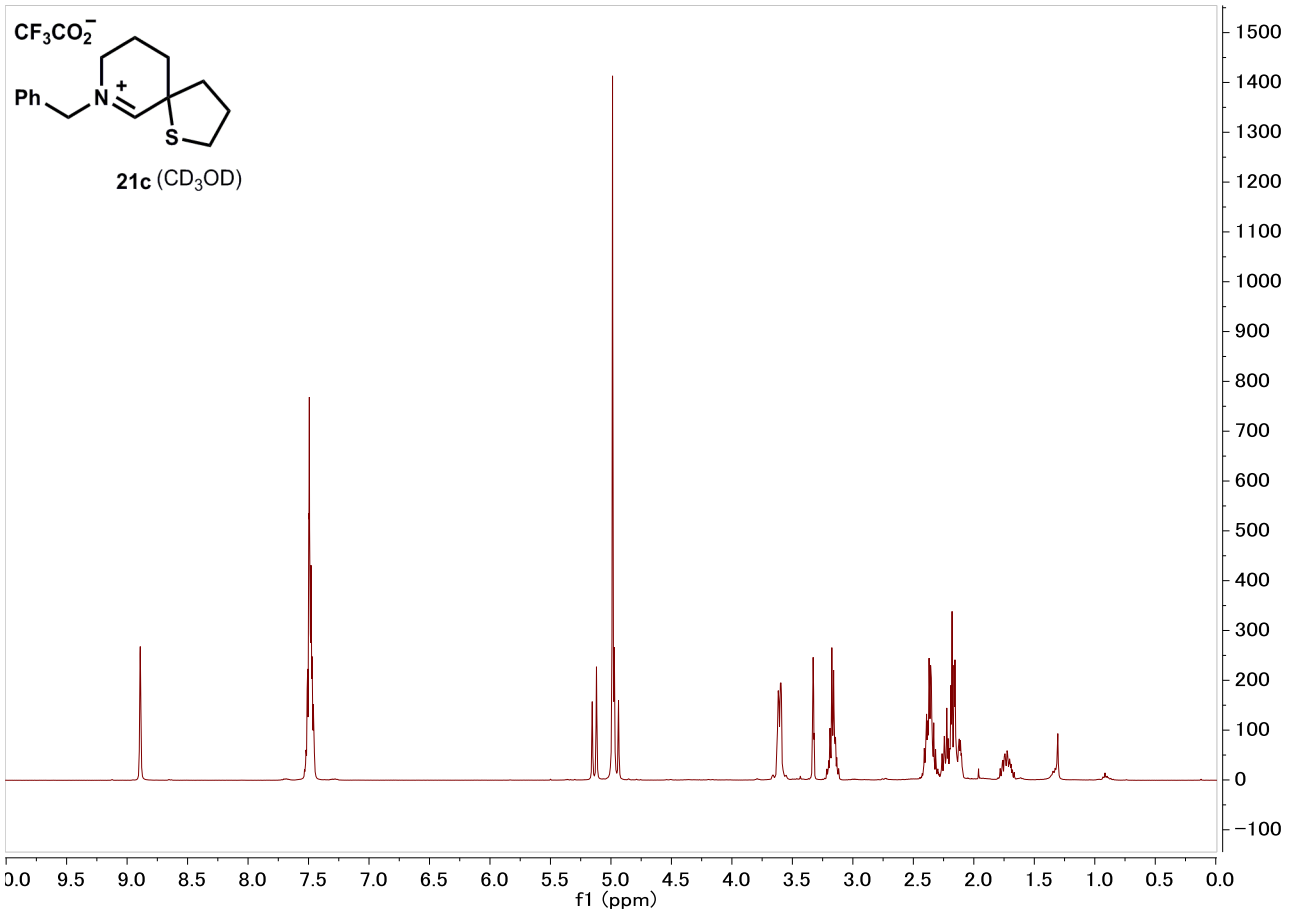
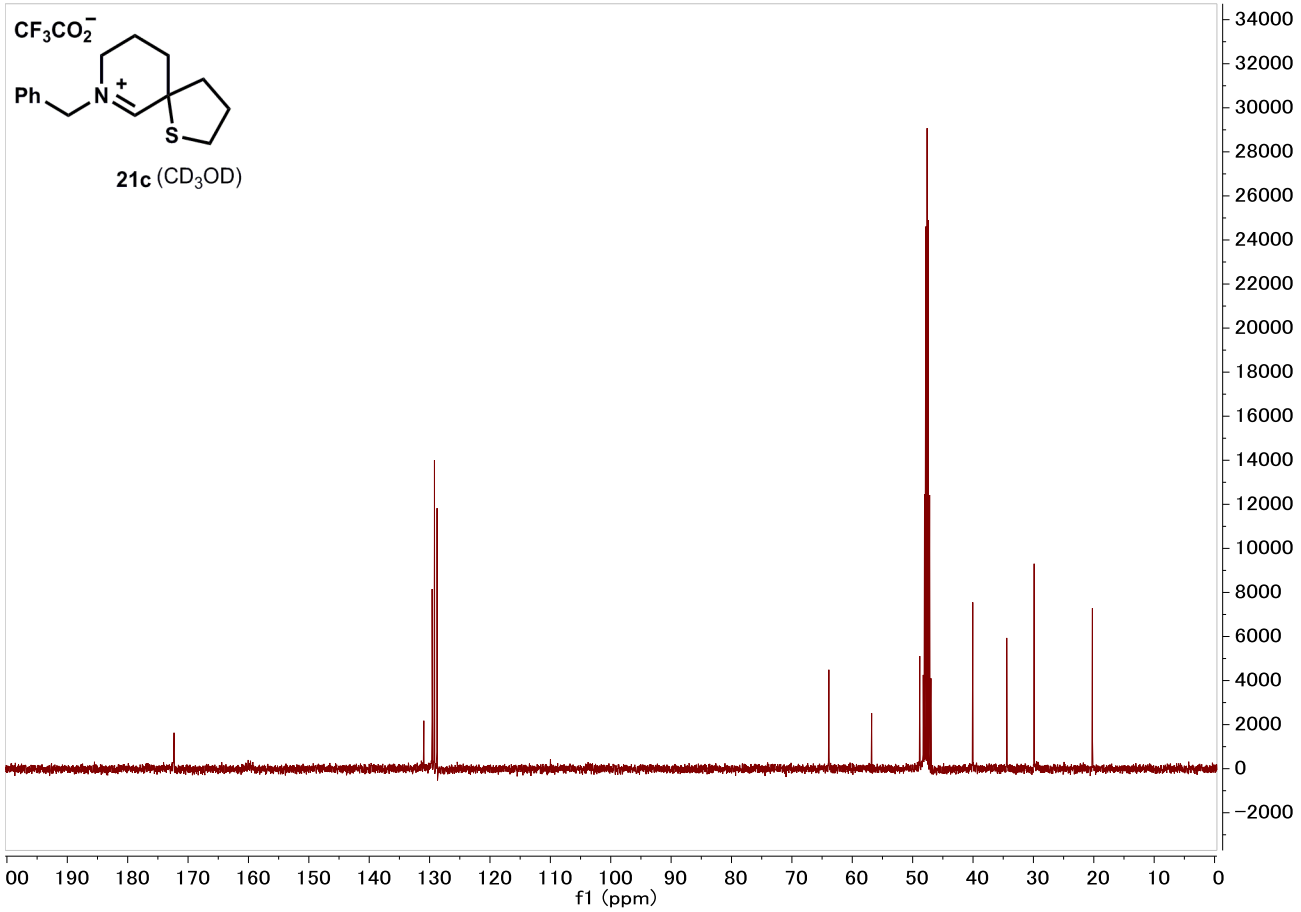
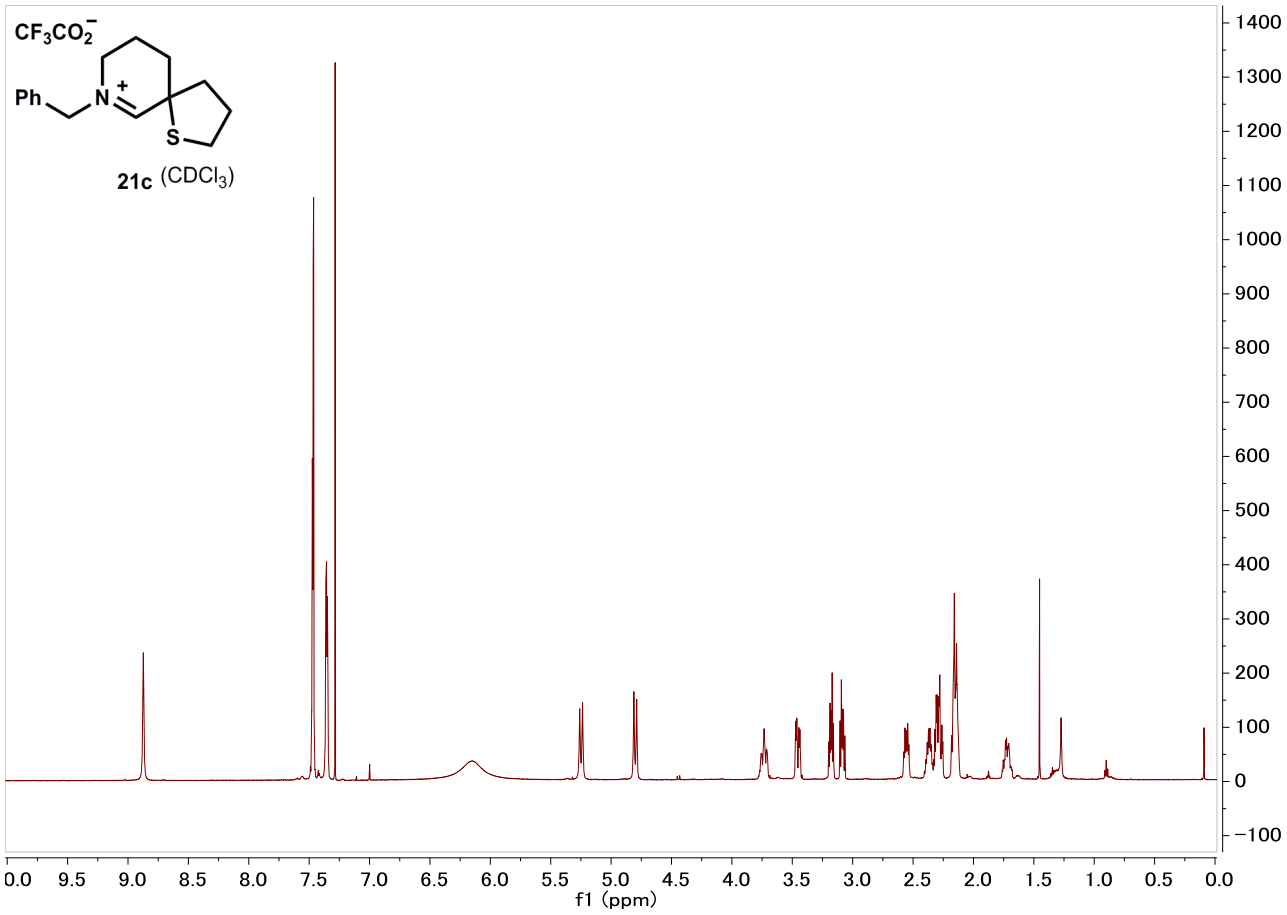
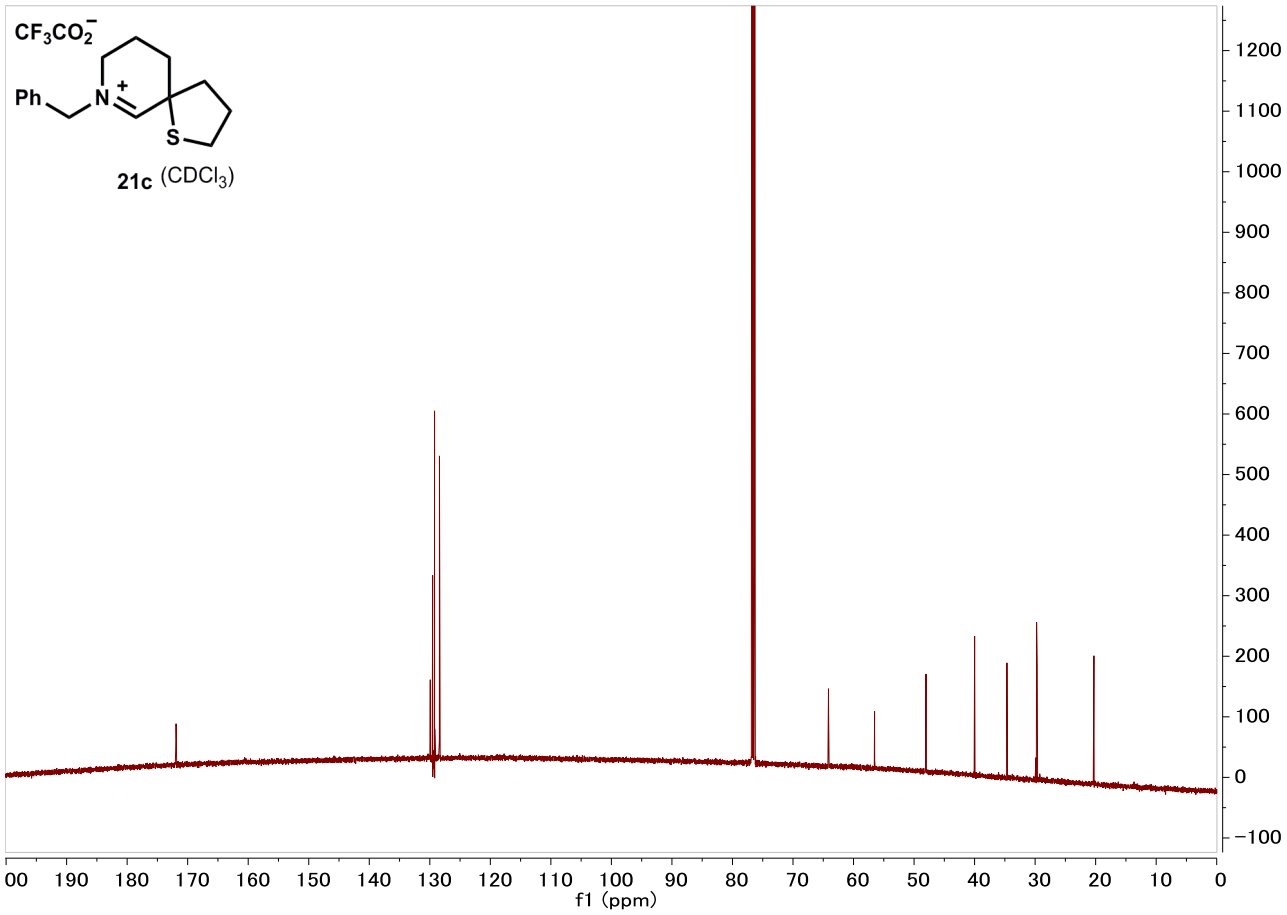
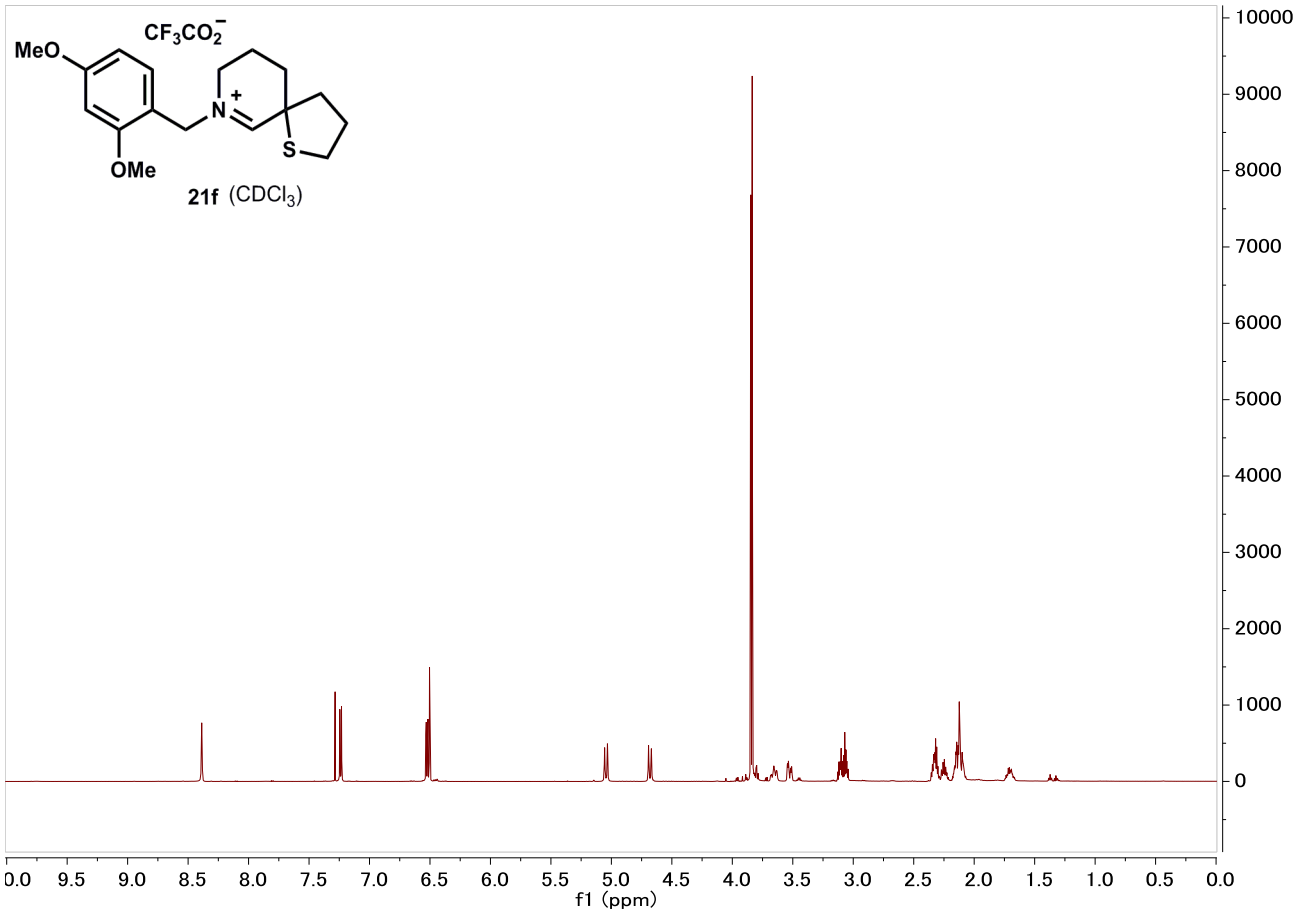
STr
SI-7c (CDCl3)
f1 (ppm)

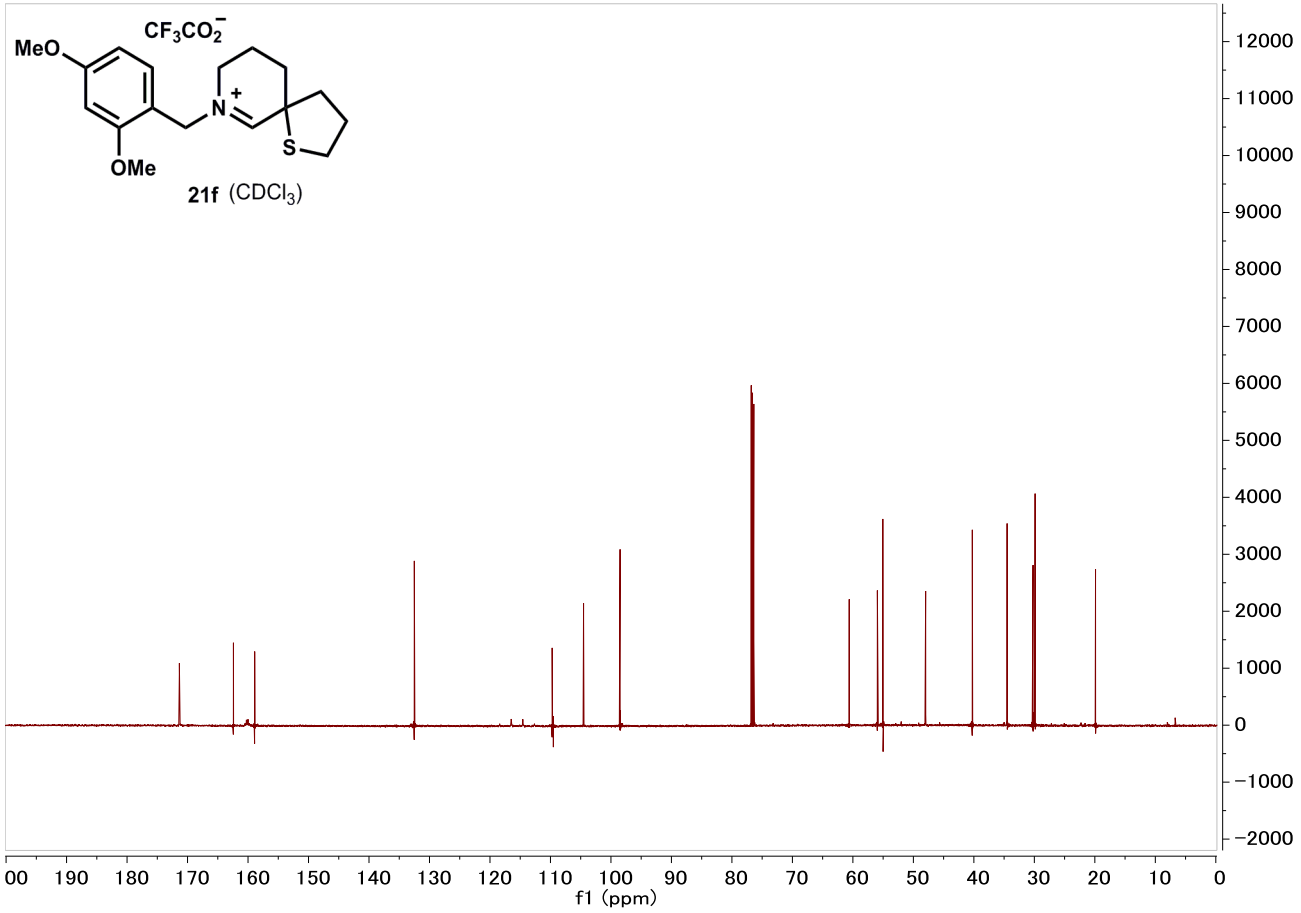

$CF_3CO_2^-$
Ph
N
+
S
21c (CD_3OD)
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

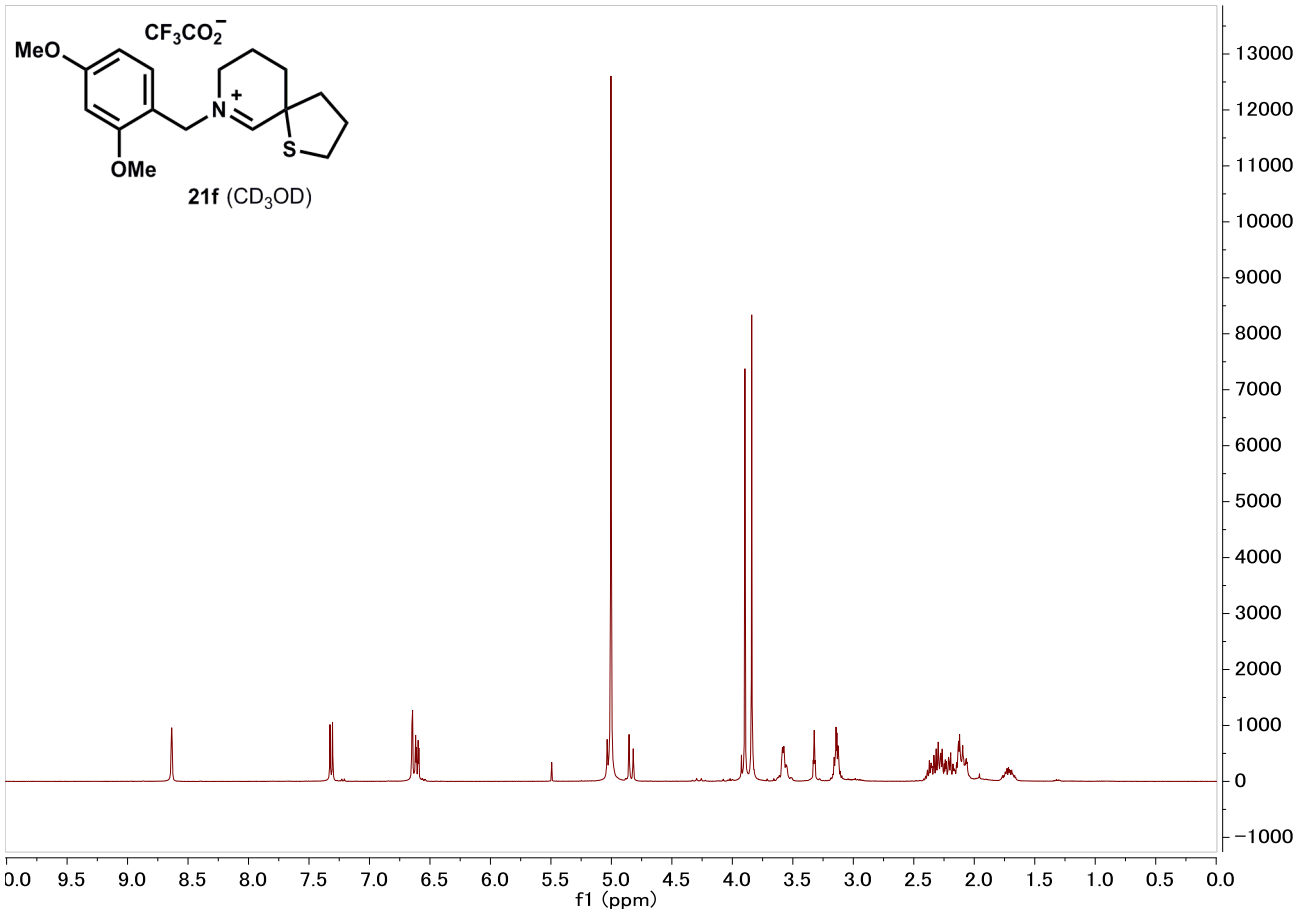

$CF_3CO_2^-$
Ph
N
+
S
21c (CD_3OD)
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
−2000
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

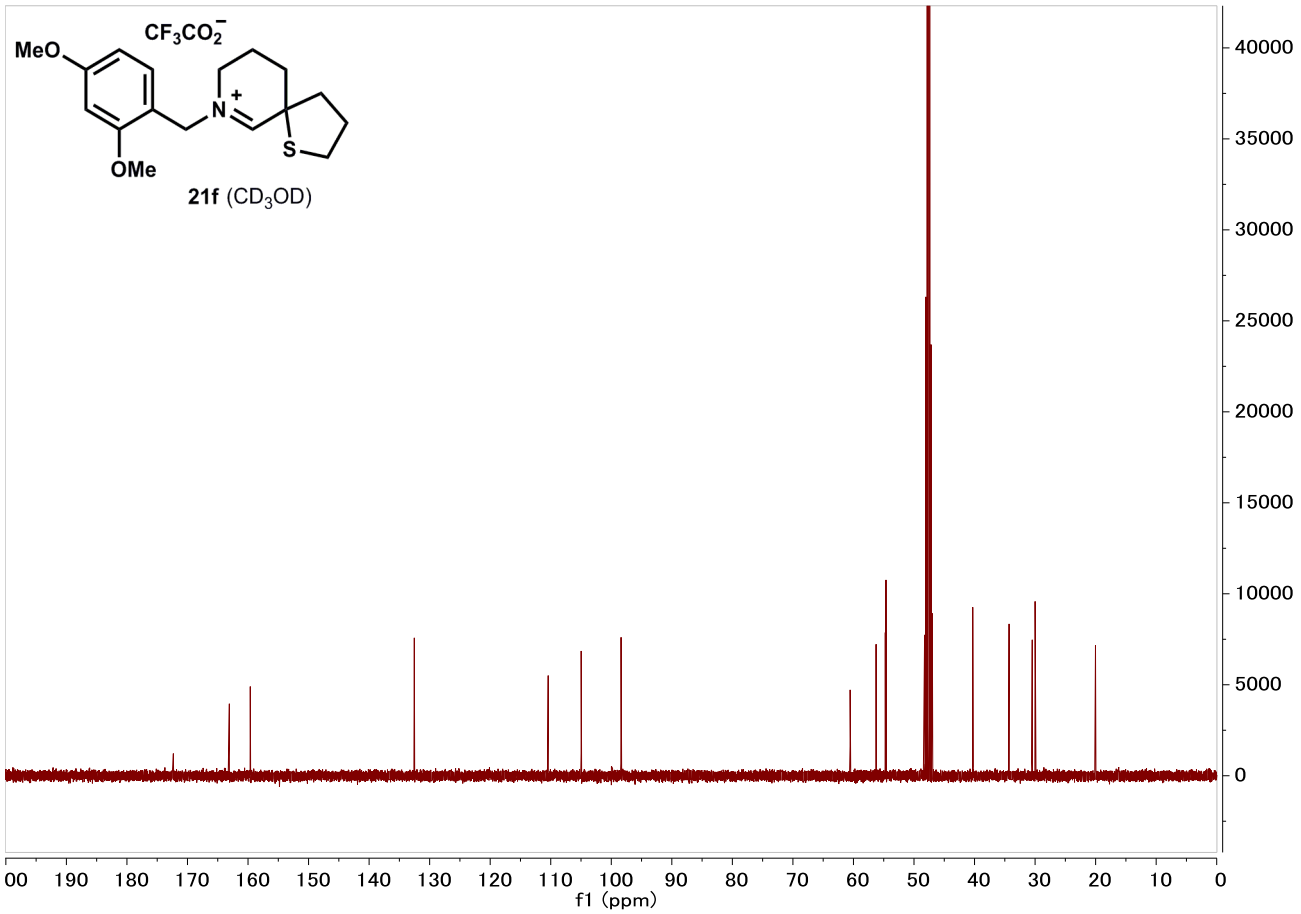

CF3CO2−
Ph
N+
S
21c (CDCl3)
f1 (ppm)

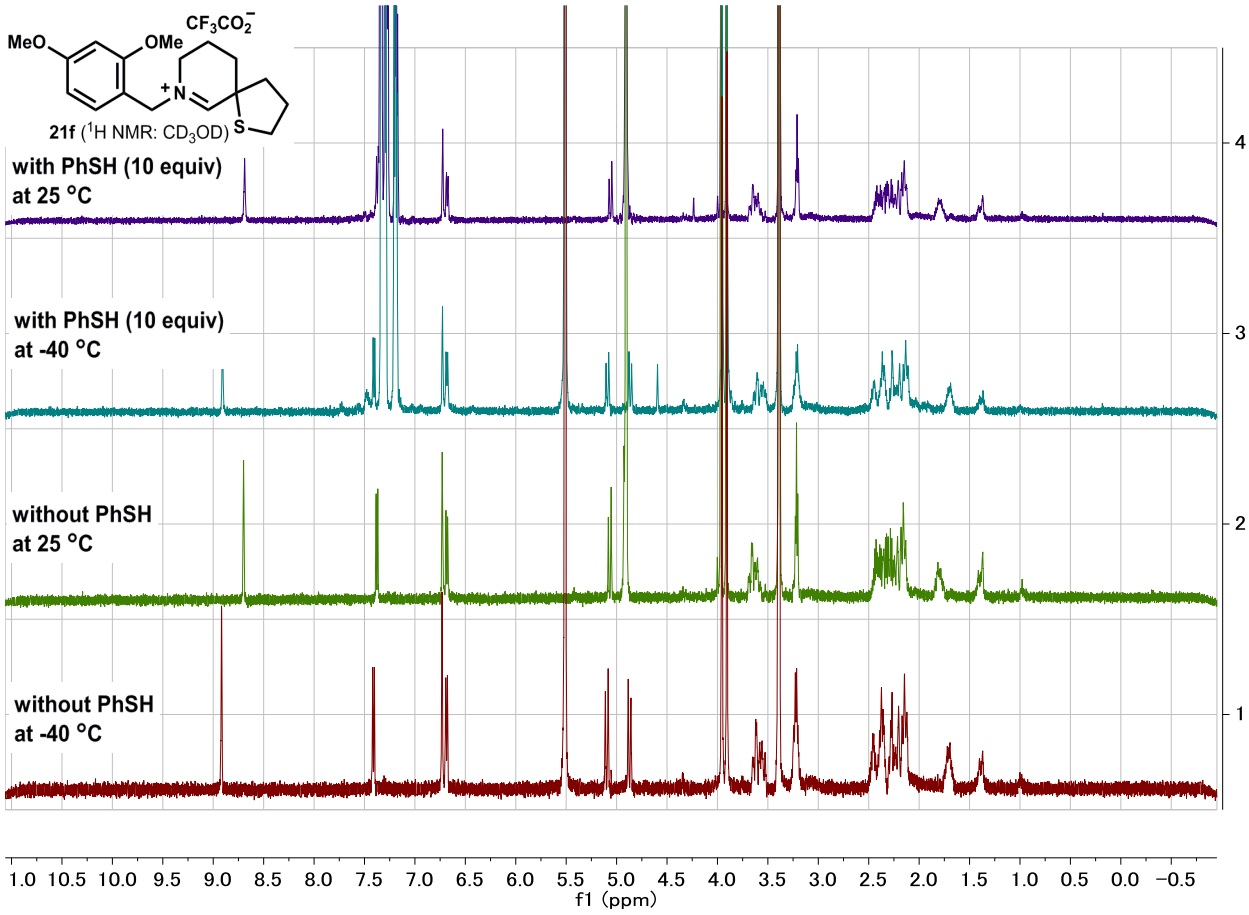

CF3CO2−
Ph
N+
S
21c (CDCl3)
f1 (ppm)

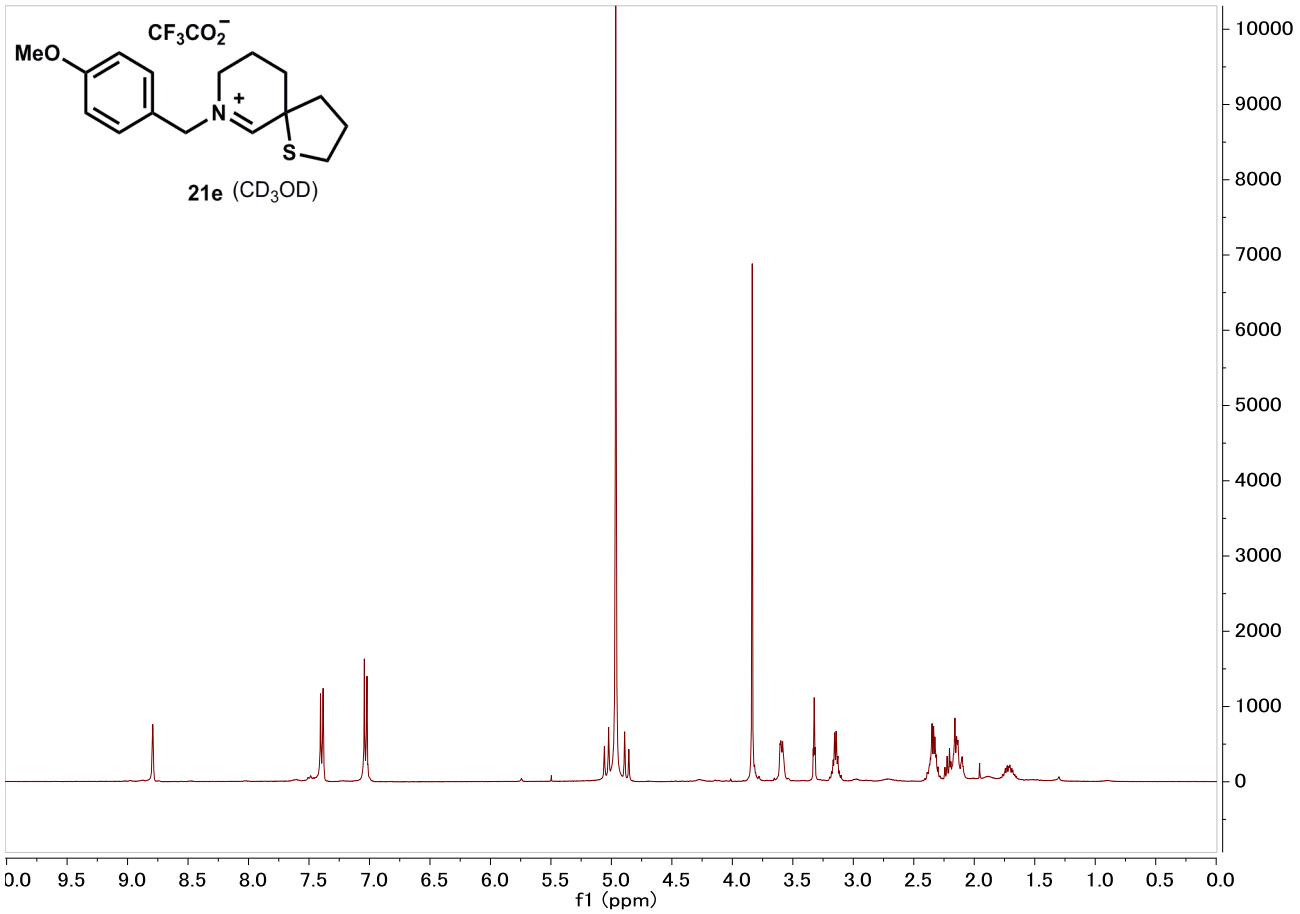

MeO
$CF_3CO_2^-$
N
+
S
OMe
21f ($CDCl_3$)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

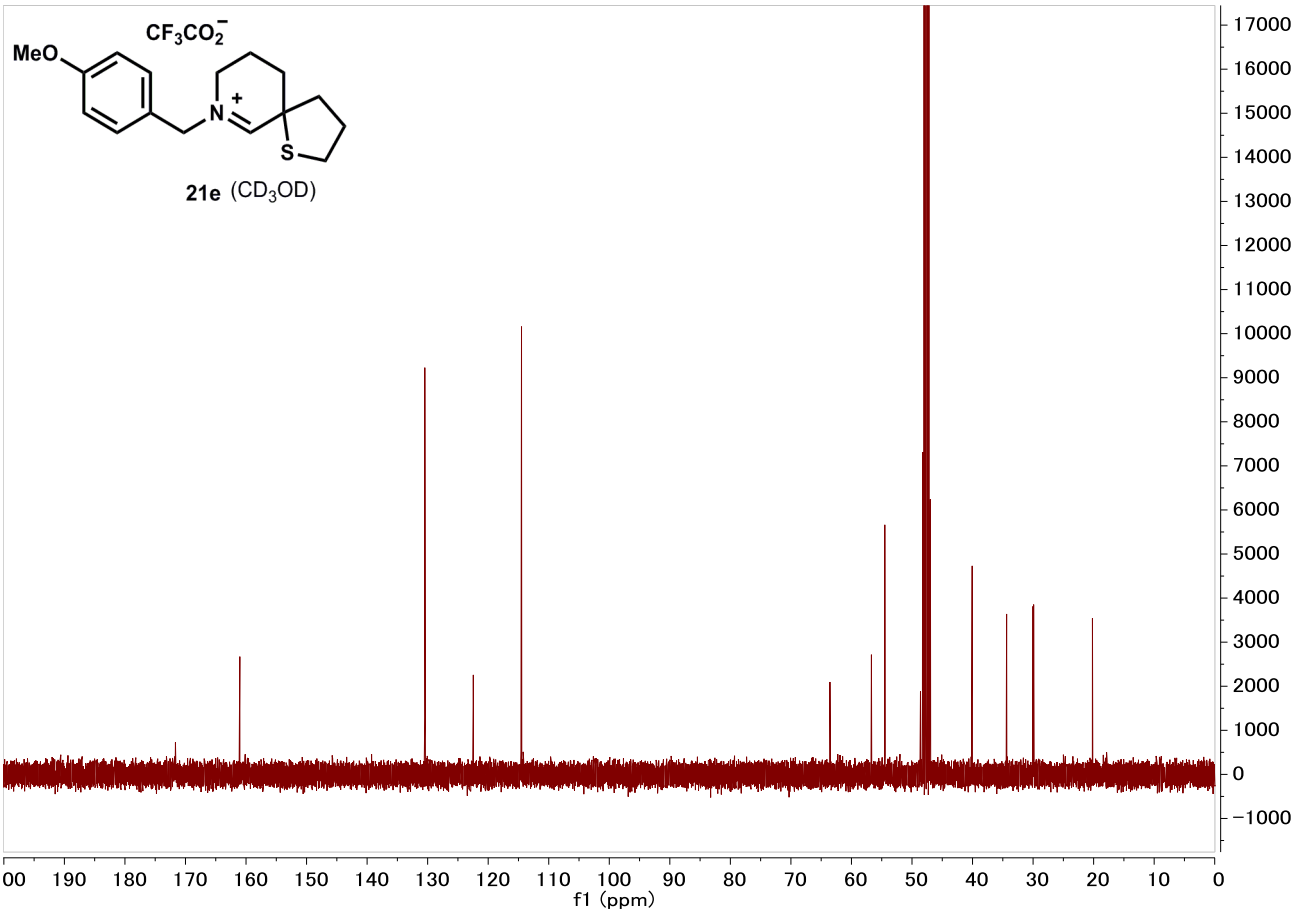

MeO
$CF_3CO_2^-$
N
+
S
OMe
21f ($CDCl_3$)
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
−2000
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

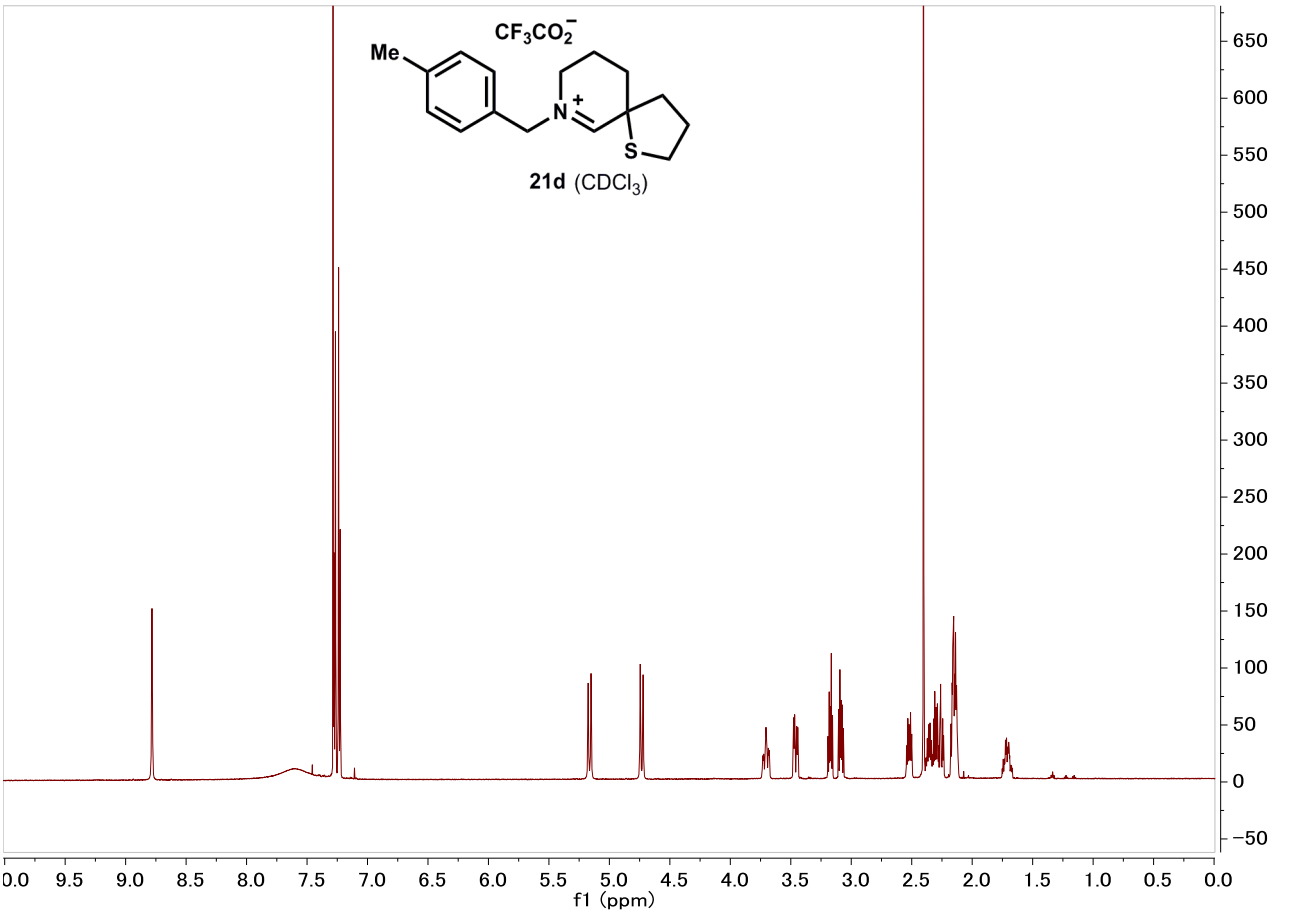

MeO
$CF_3CO_2^-$
N
S
OMe
21f (CD_3OD)
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

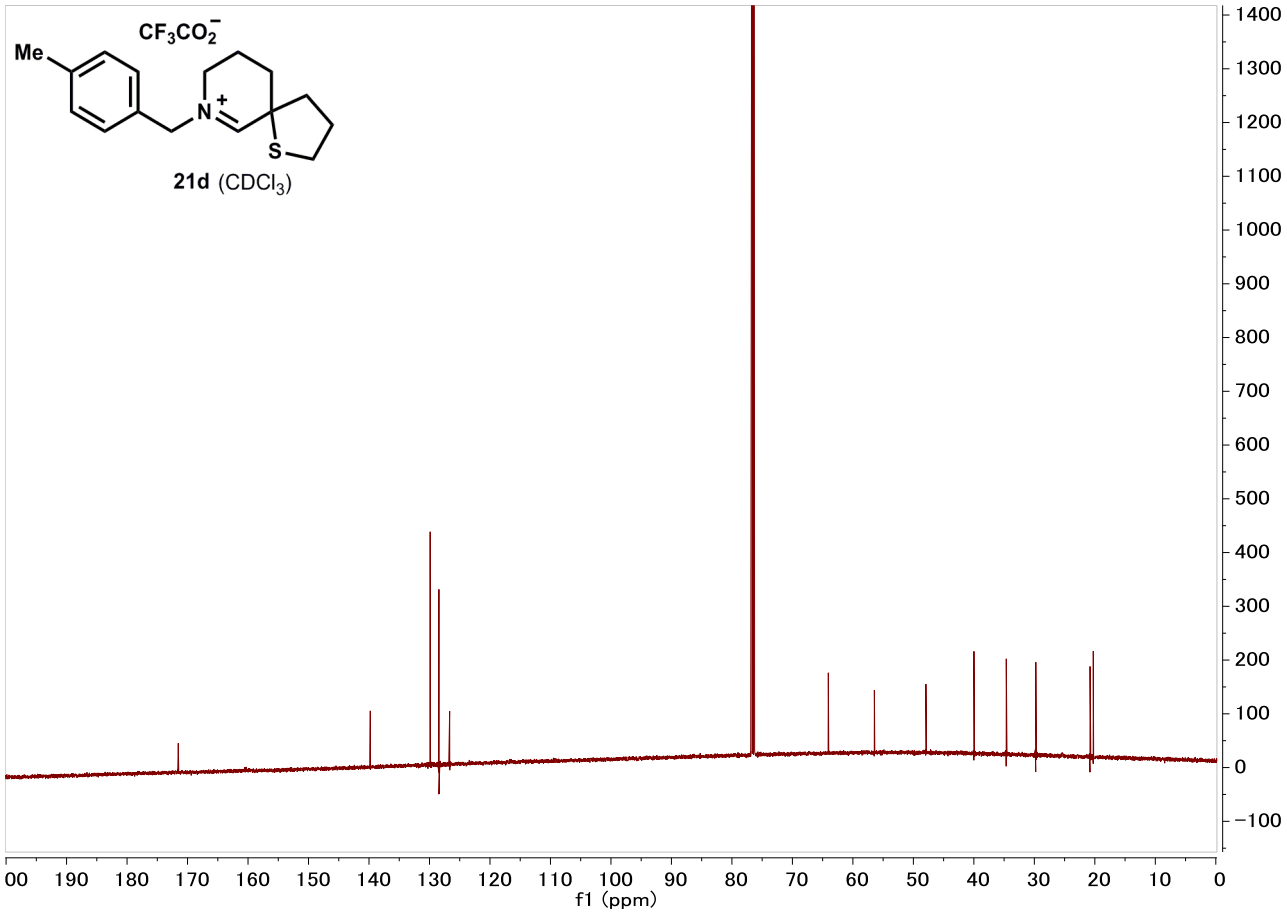

MeO
$CF_3CO_2^-$
N
S
OMe
21f (CD_3OD)
40000
35000
30000
25000
20000
15000
10000
5000
0
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

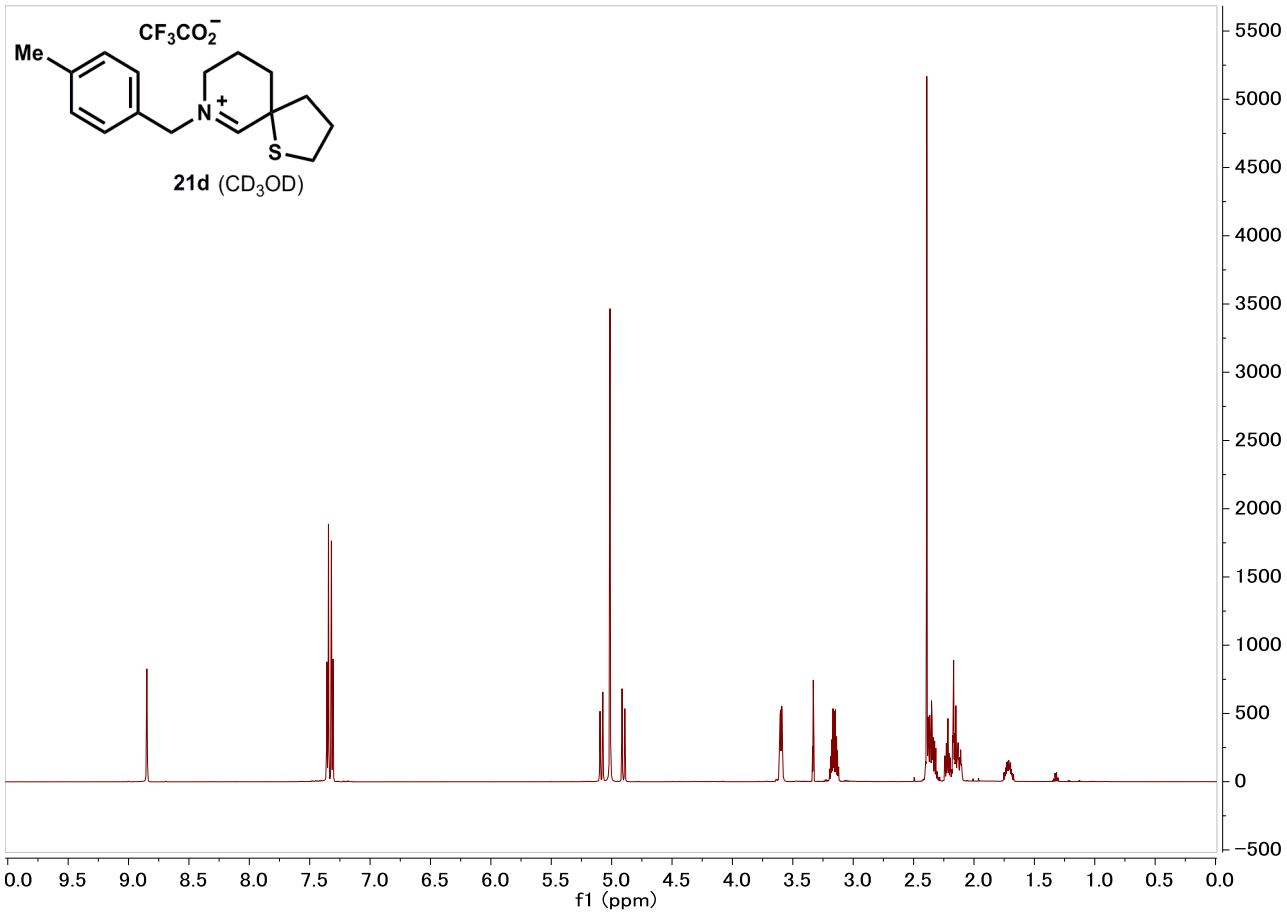

MeO
OMe
CF3CO2−
+N
S
21f (1H NMR: CD3OD)
with PhSH (10 equiv)
at 25 °C
with PhSH (10 equiv)
at -40 °C
without PhSH
at 25 °C
without PhSH
at -40 °C
4
3
2
1
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

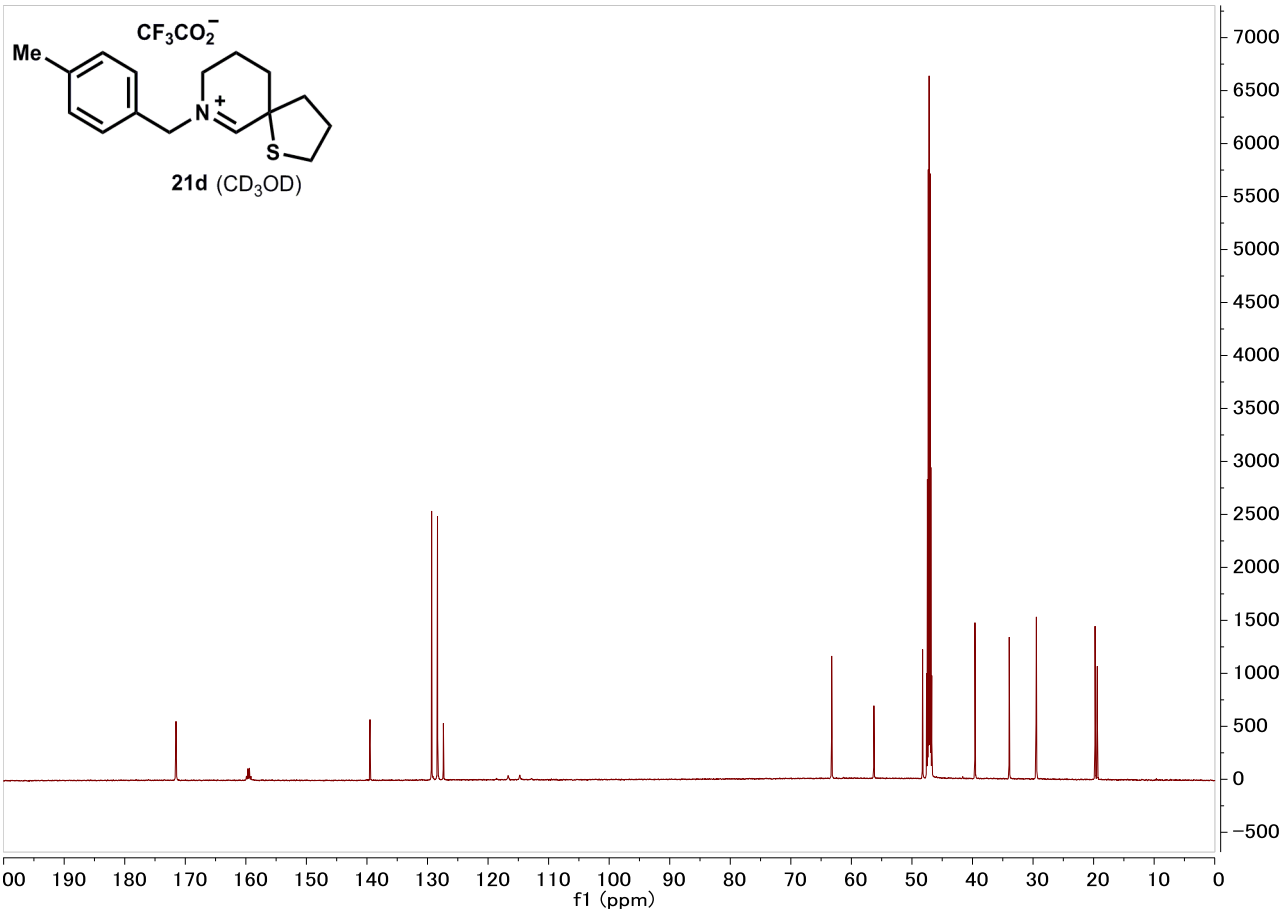

MeO
CF3CO2−
+N
S
21e (CD3OD)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

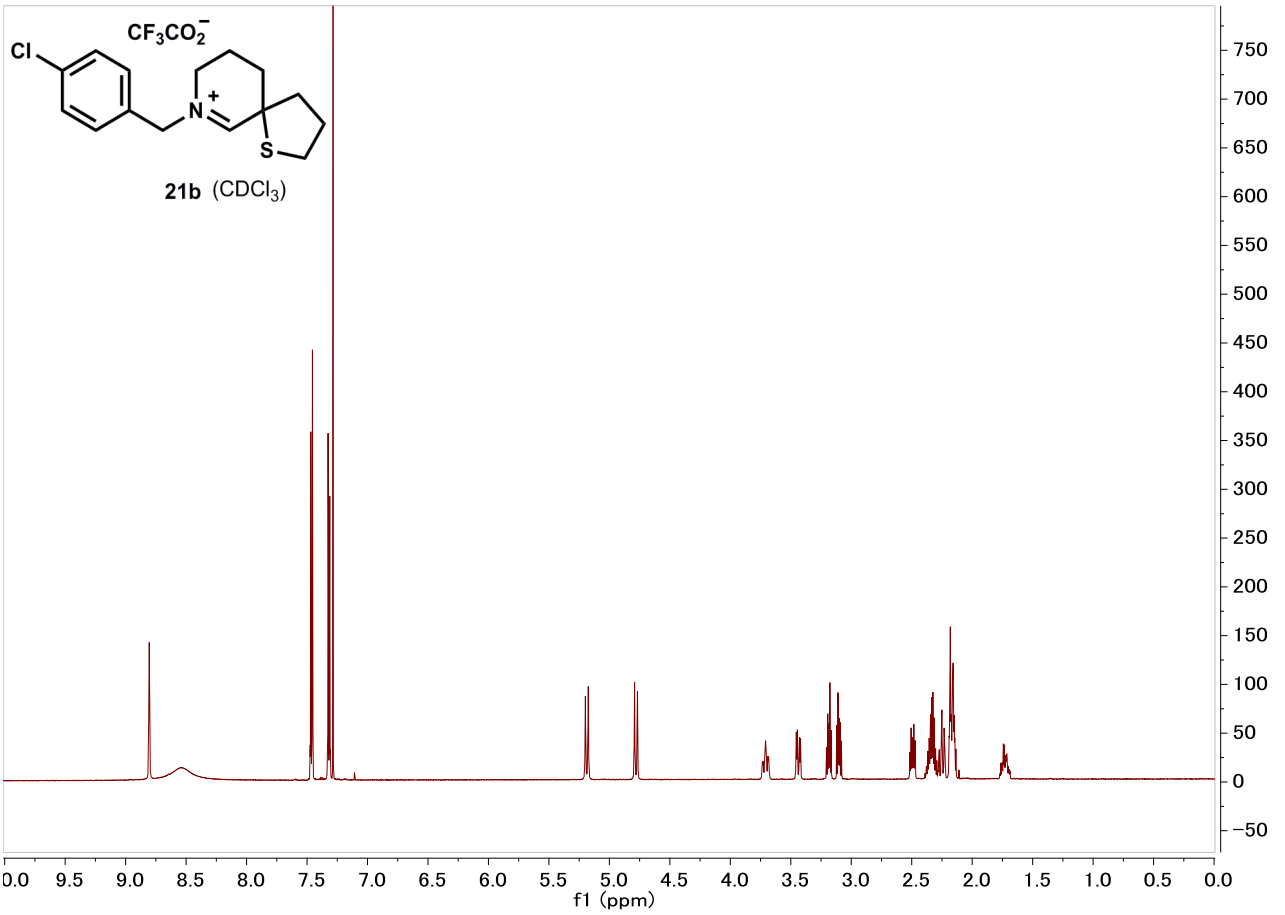

MeO
$CF_3CO_2^-$
N+
S
21e (CD_3OD)
f1 (ppm)

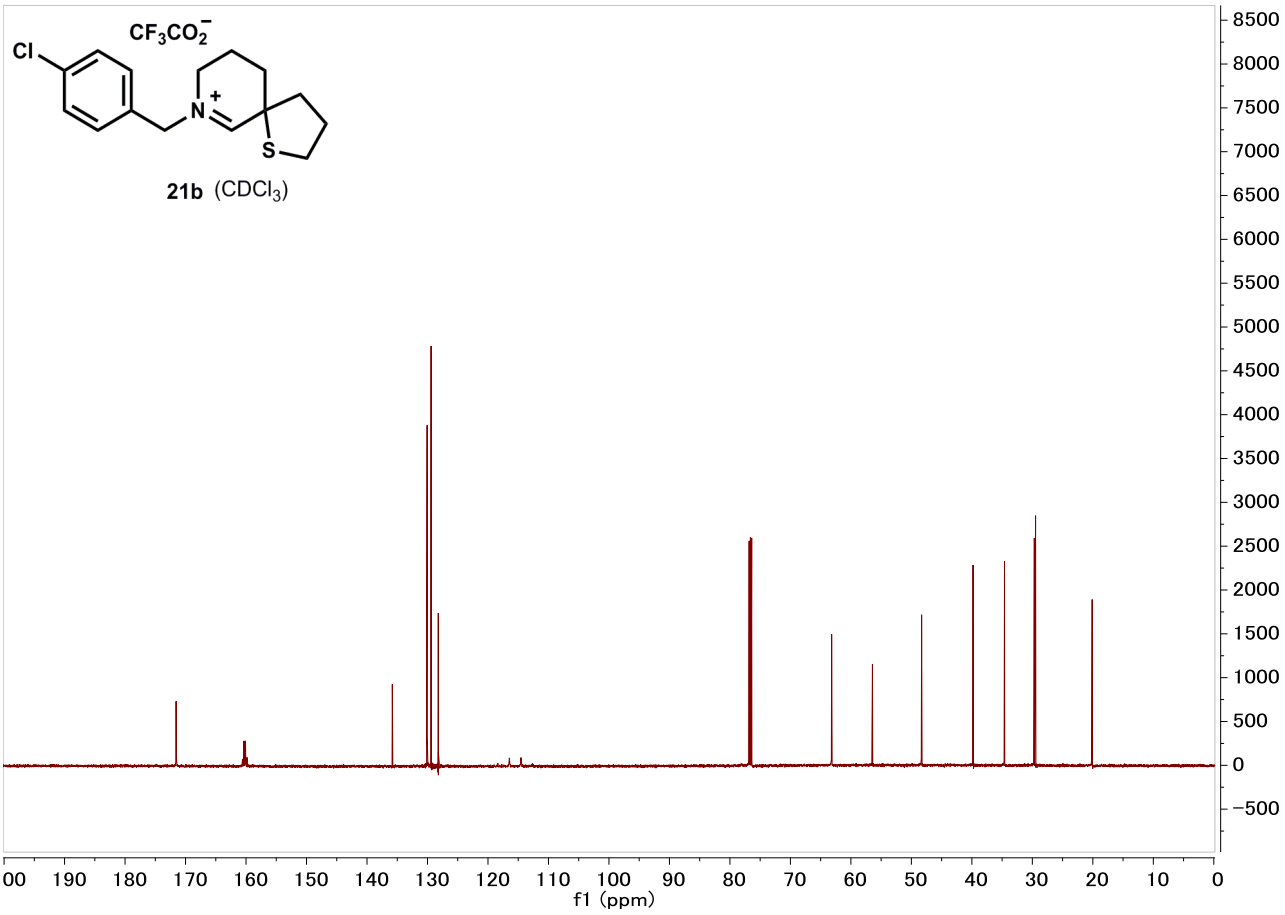

Me
$CF_3CO_2^-$
N+
S
21d ($CDCl_3$)
f1 (ppm)

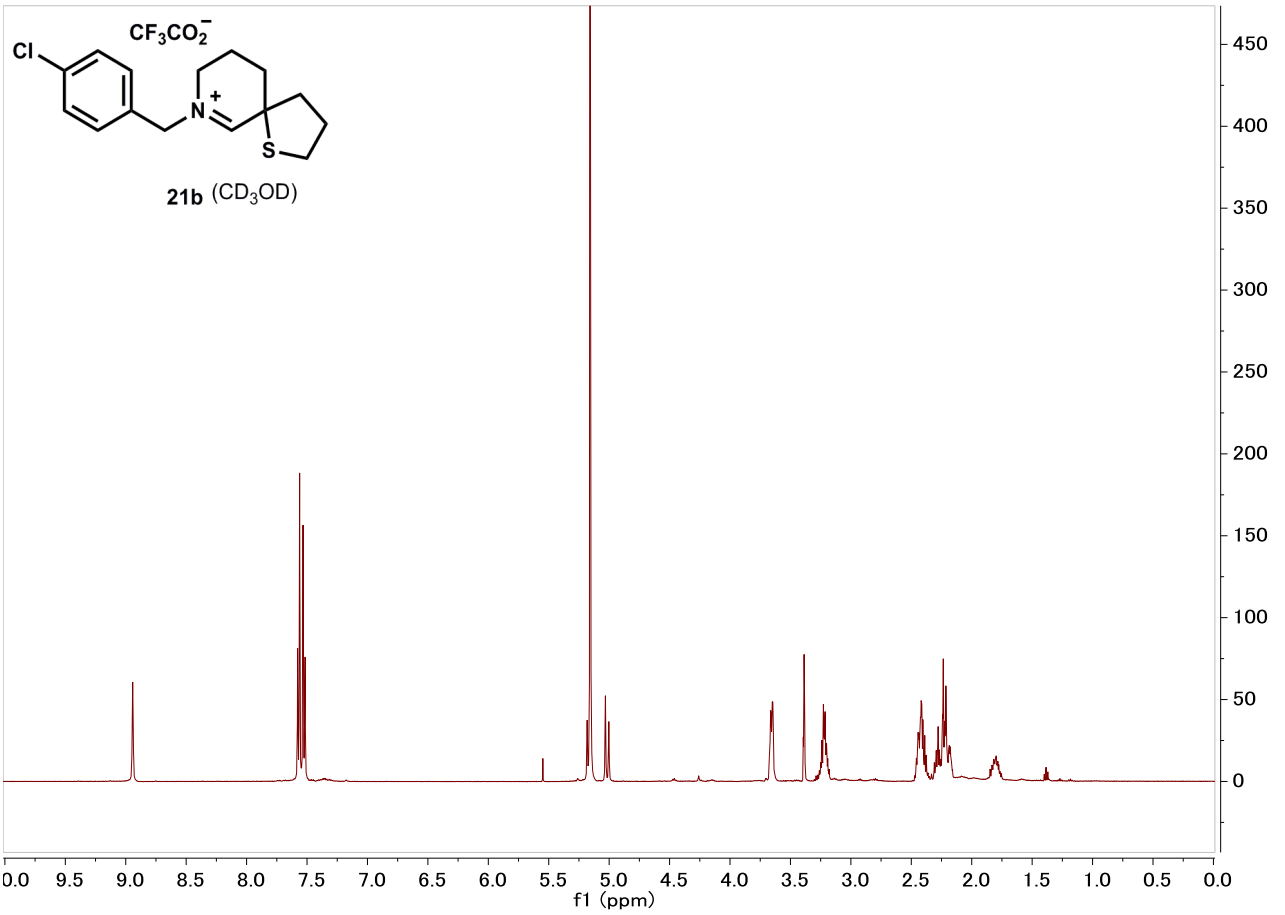

Me
$CF_3CO_2^-$
N+
S
21d ($CDCl_3$)
f1 (ppm)

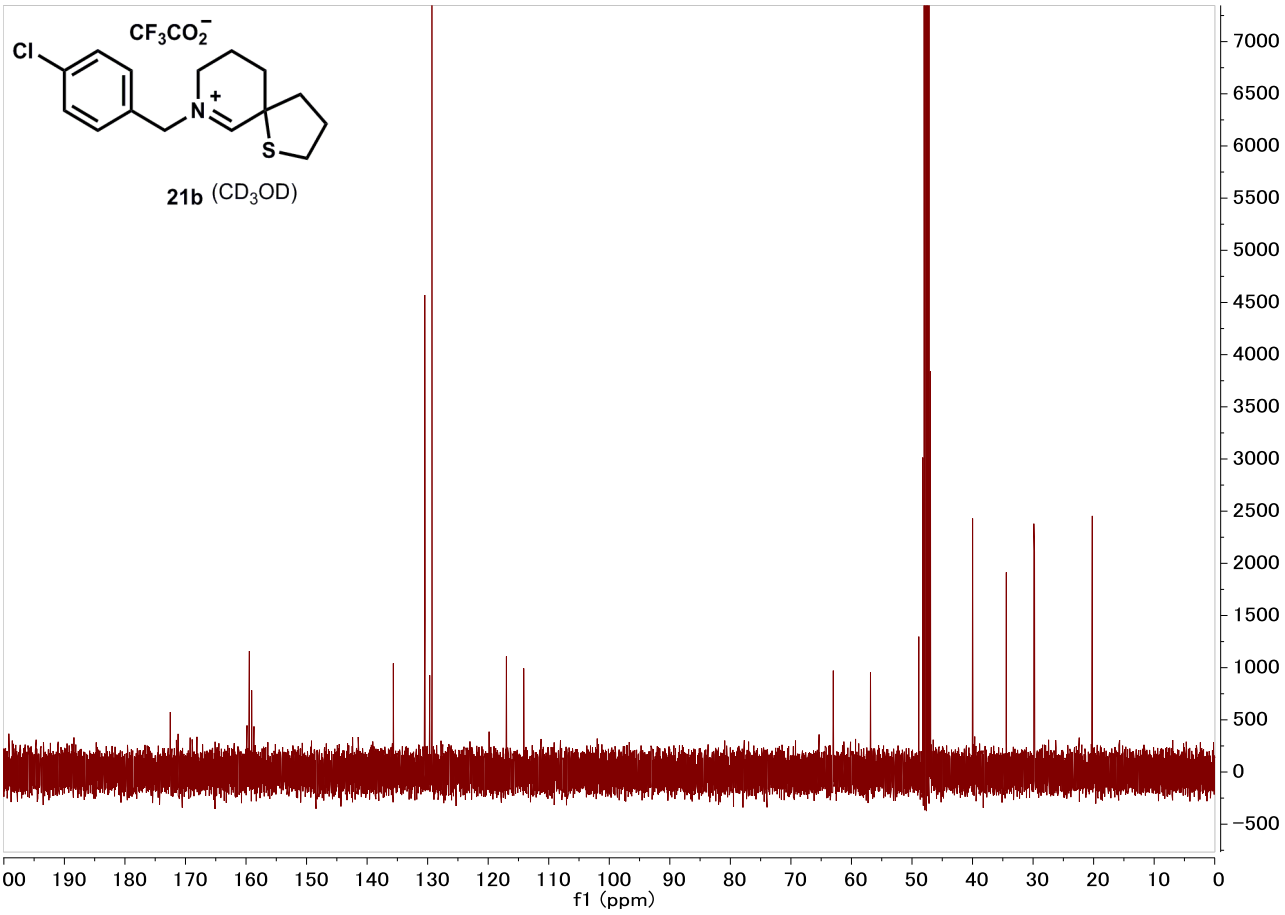

Me
$CF_3CO_2^-$
N+
S
21d (CD_3OD)
f1 (ppm)

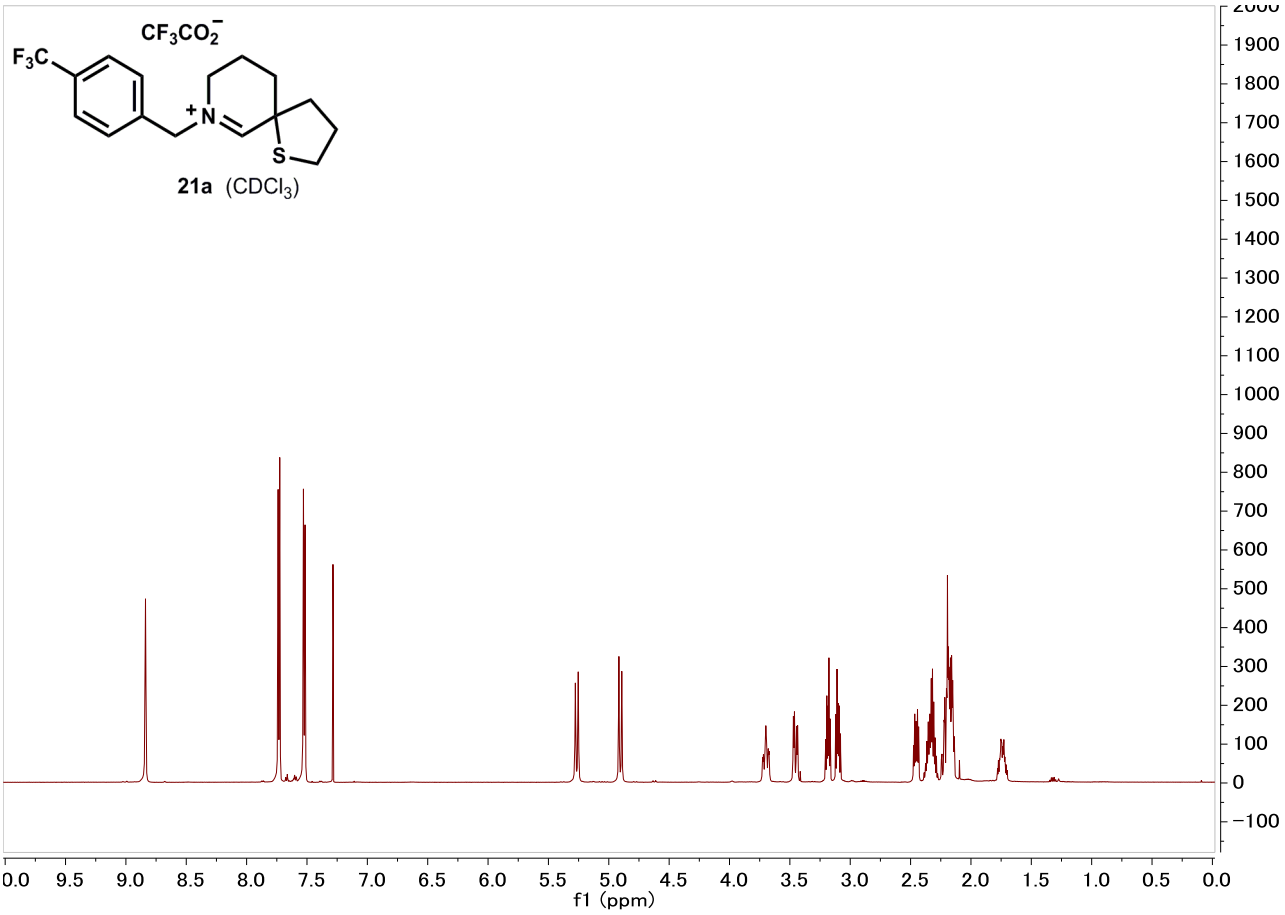

Me
$CF_3CO_2^-$
N+
S
21d (CD_3OD)
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

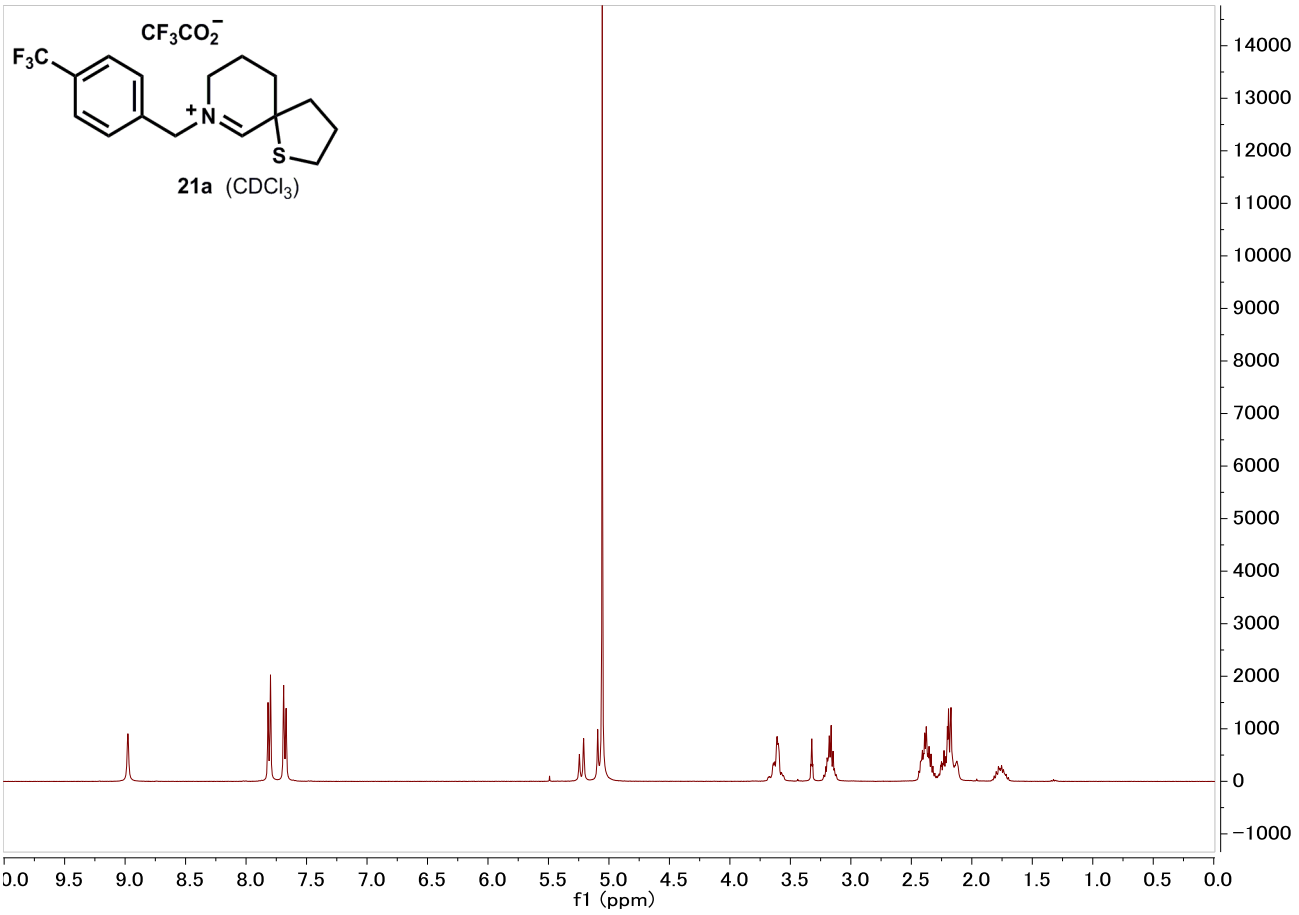

Cl
$CF_3CO_2^-$
N+
S
21b ($CDCl_3$)
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
−50
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

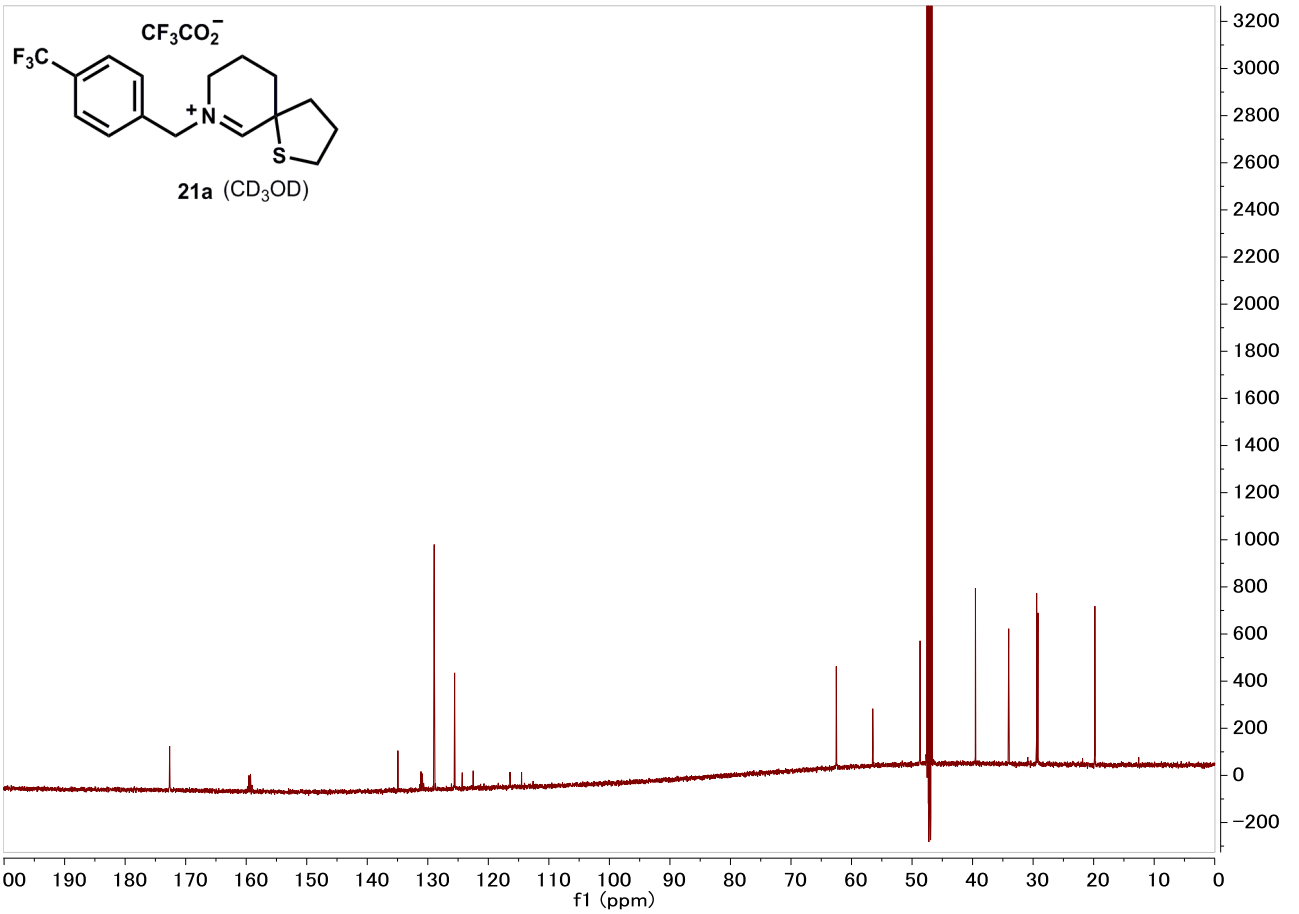

CF3CO2−
Cl
N+
S
21b (CDCl3)
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

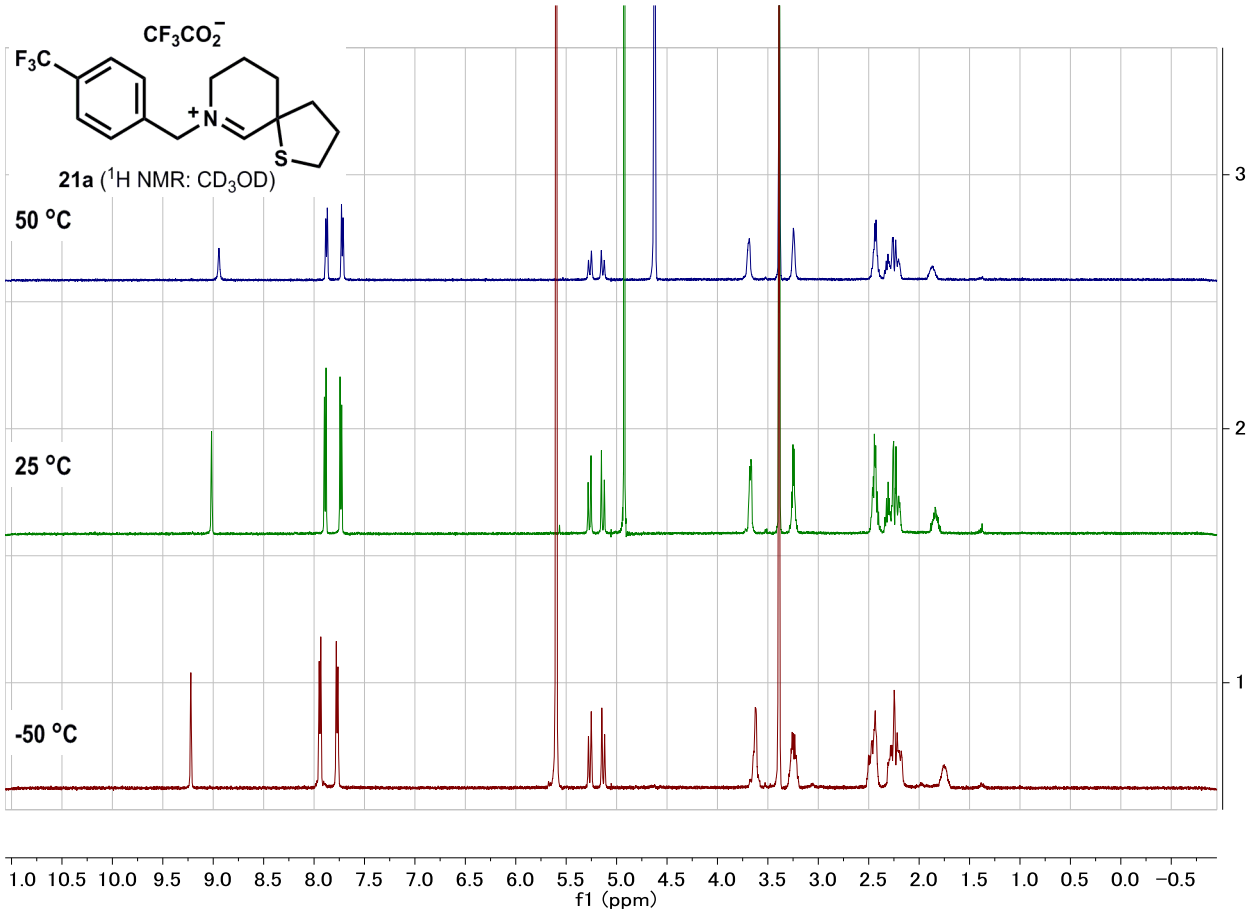

CF3CO2−
Cl
N+
S
21b (CD3OD)
450
400
350
300
250
200
150
100
50
0
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

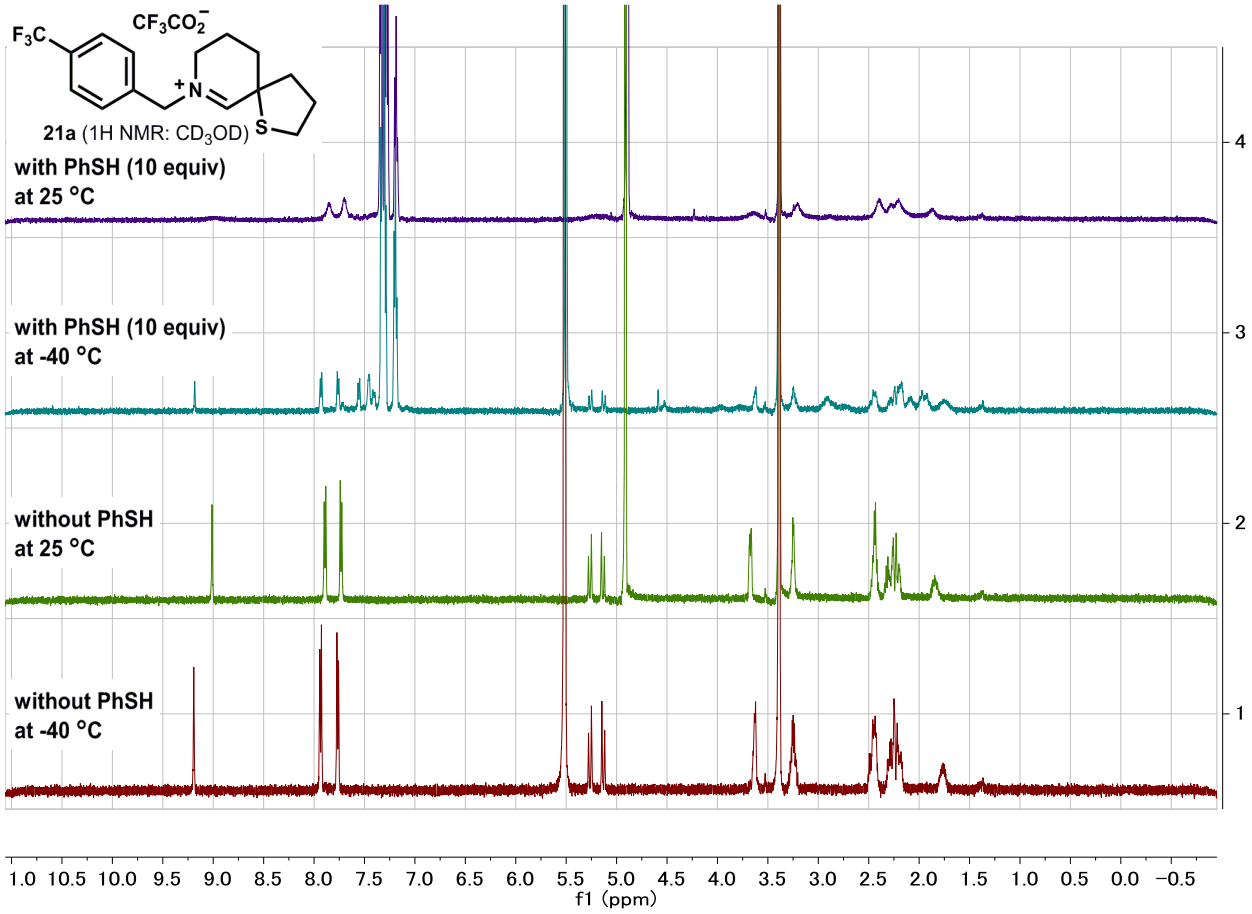

CF3CO2−
Cl
N+
S
21b (CD3OD)
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

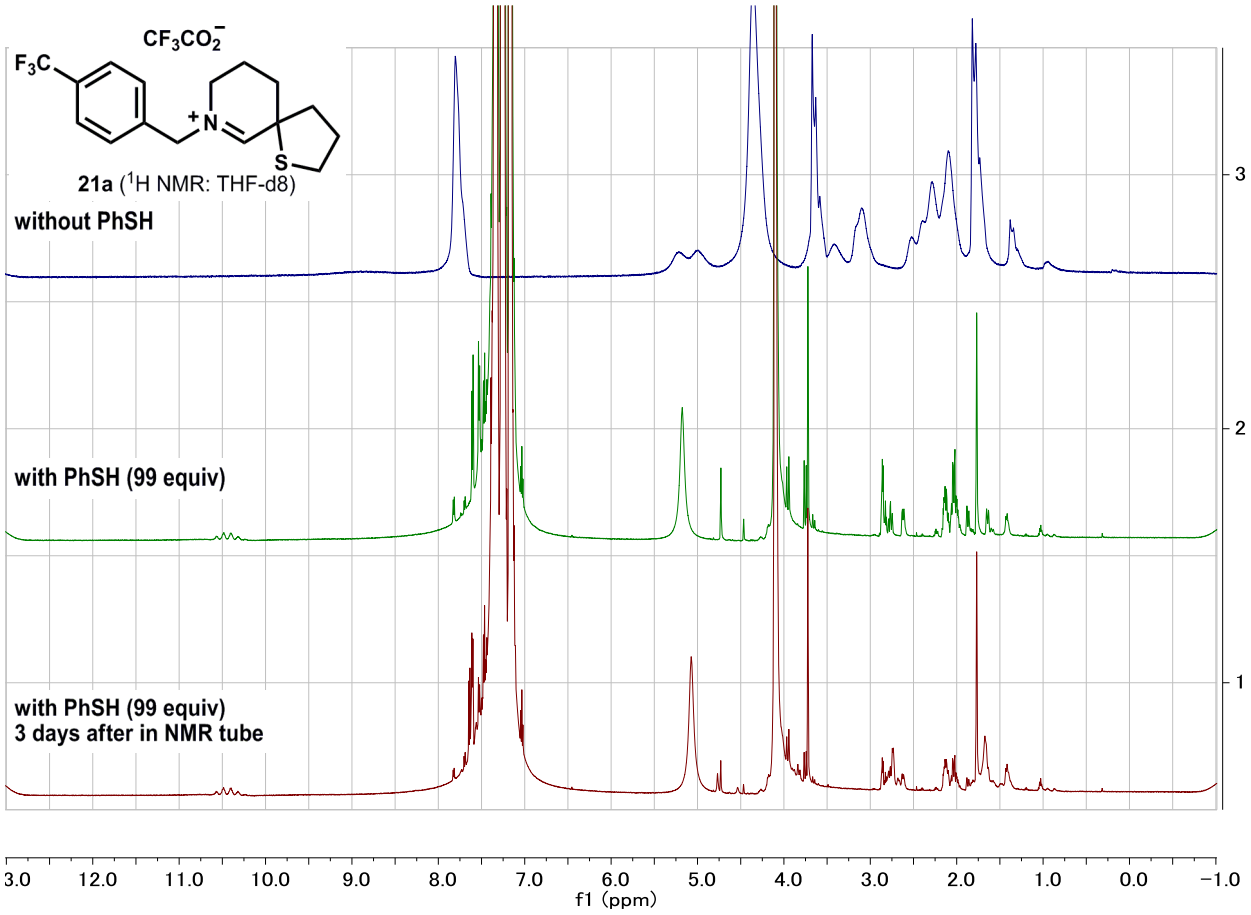

CF3CO2−
F3C
N+
S
21a (CDCl3)
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

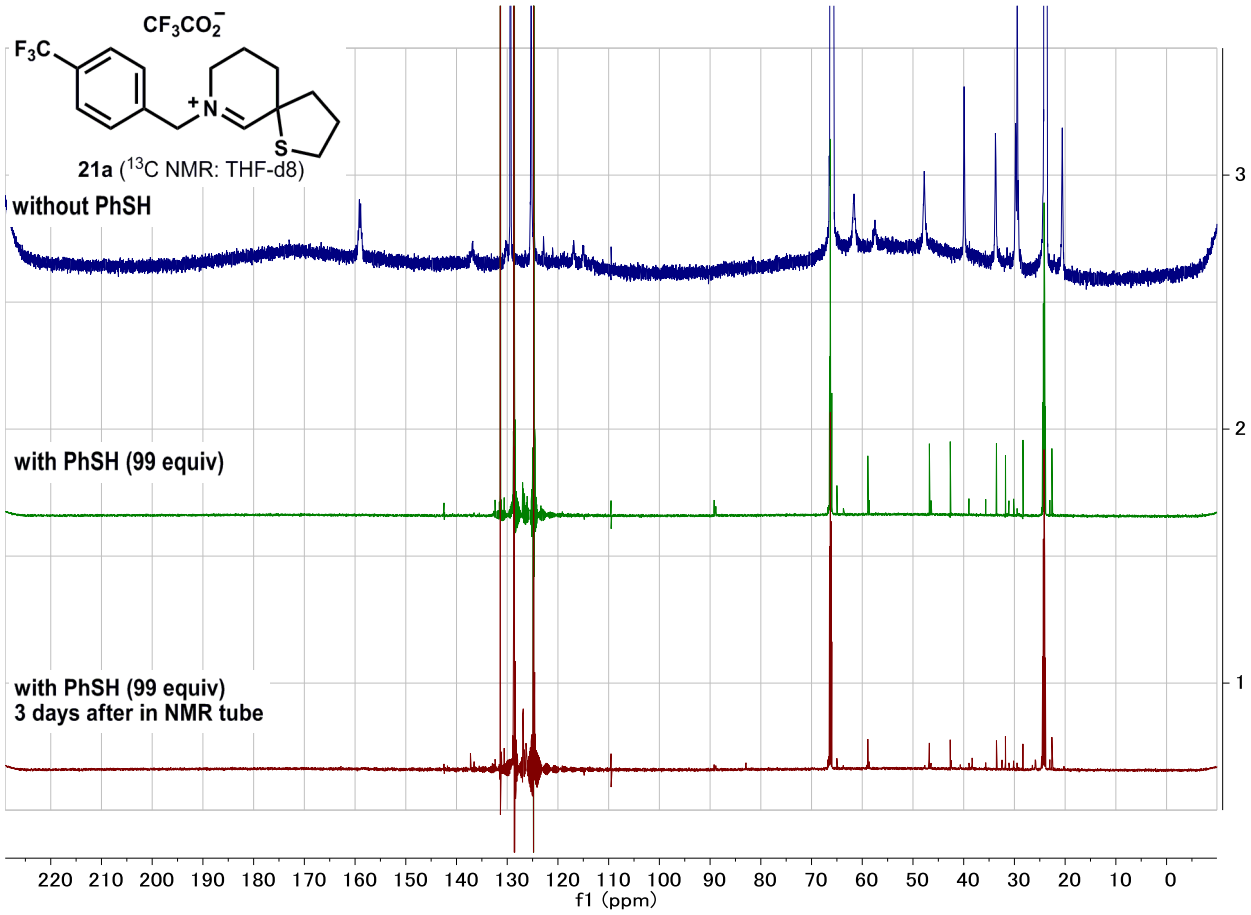

CF3CO2−
F3C
+N
S
21a (CDCl3)
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

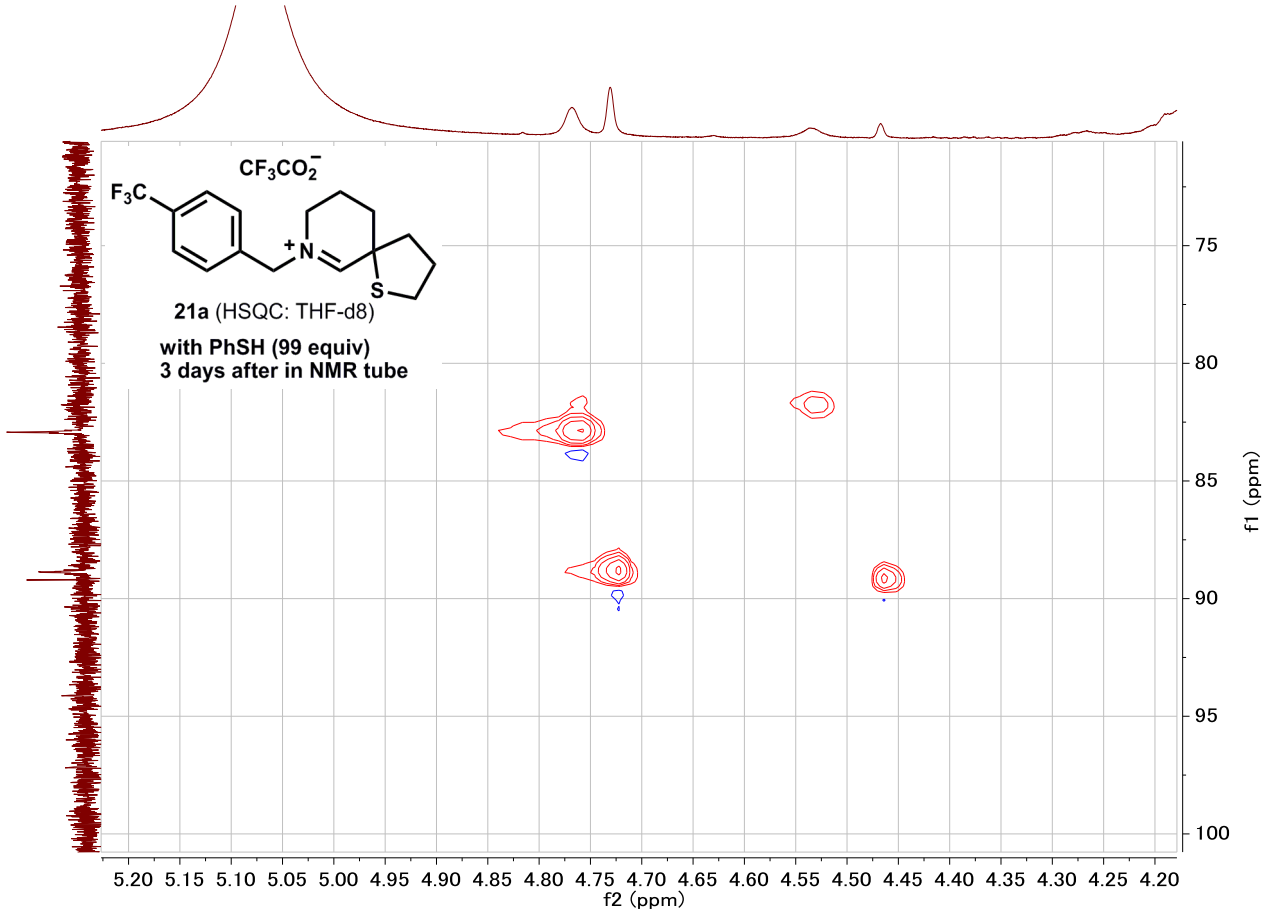

CF3CO2−
F3C
+N
S
21a (CD3OD)
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

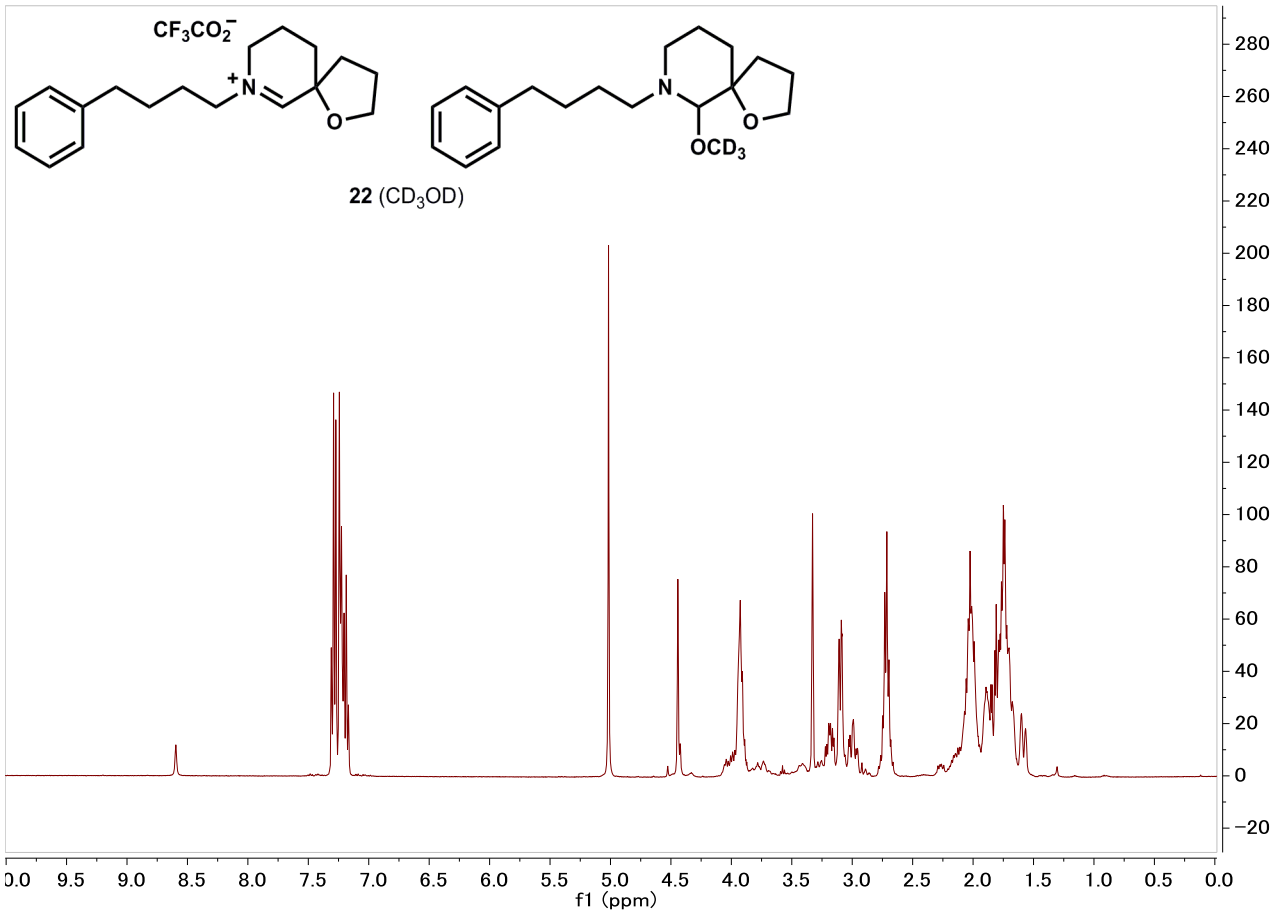

CF3CO2−
F3C
+N
S
21a (1H NMR: CD3OD)
50 °C
25 °C
-50 °C
3
2
1
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

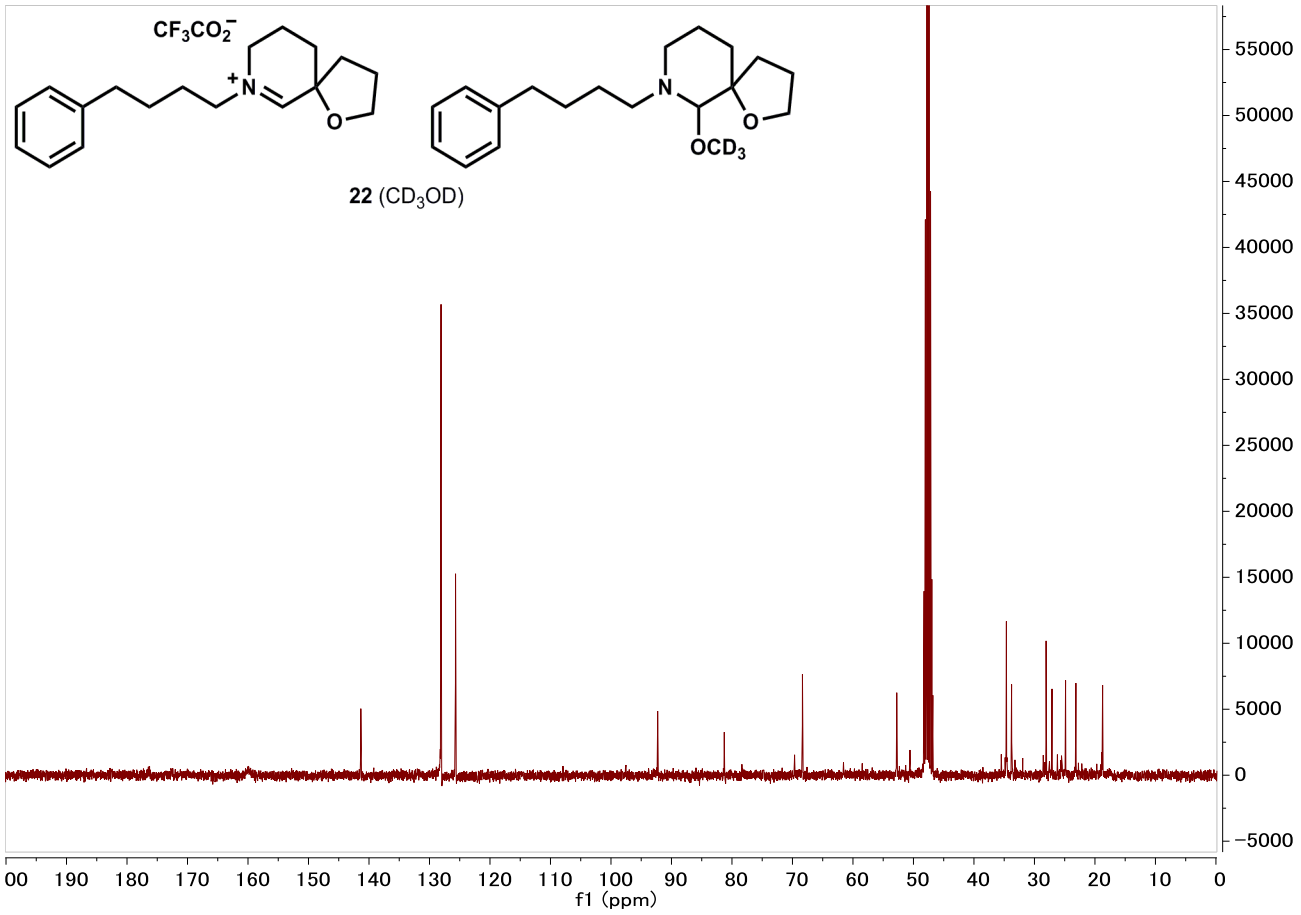

CF3CO2−
F3C
+N
S
21a (1H NMR: CD3OD)
with PhSH (10 equiv)
at 25 °C
with PhSH (10 equiv)
at -40 °C
without PhSH
at 25 °C
without PhSH
at -40 °C
4
3
2
1
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

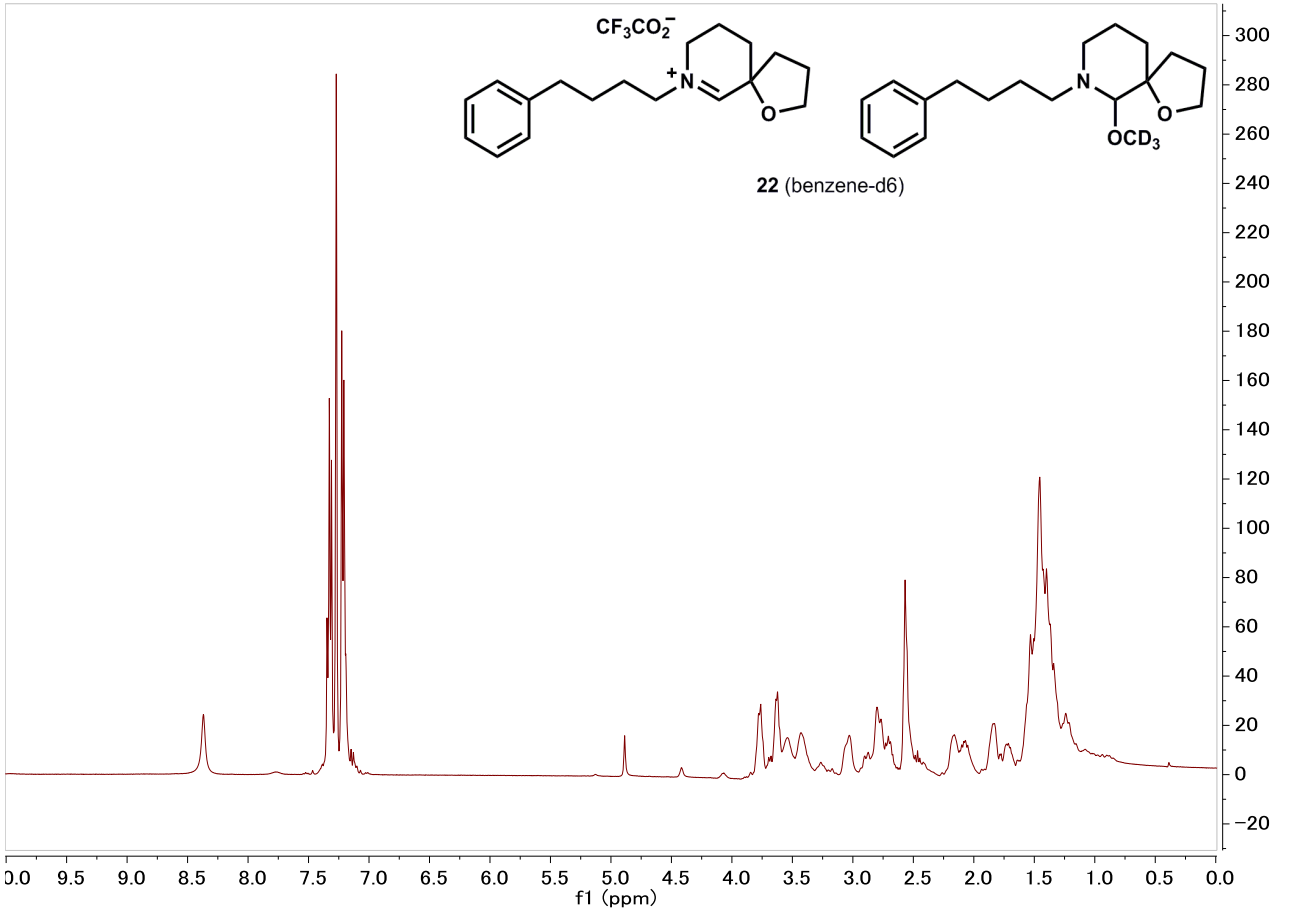

CF3CO2−
F3C
+N
S
21a (1H NMR: THF-d8)
without PhSH
with PhSH (99 equiv)
with PhSH (99 equiv)
3 days after in NMR tube
3
2
1
3.0 12.0 11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 −1.0
f1 (ppm)

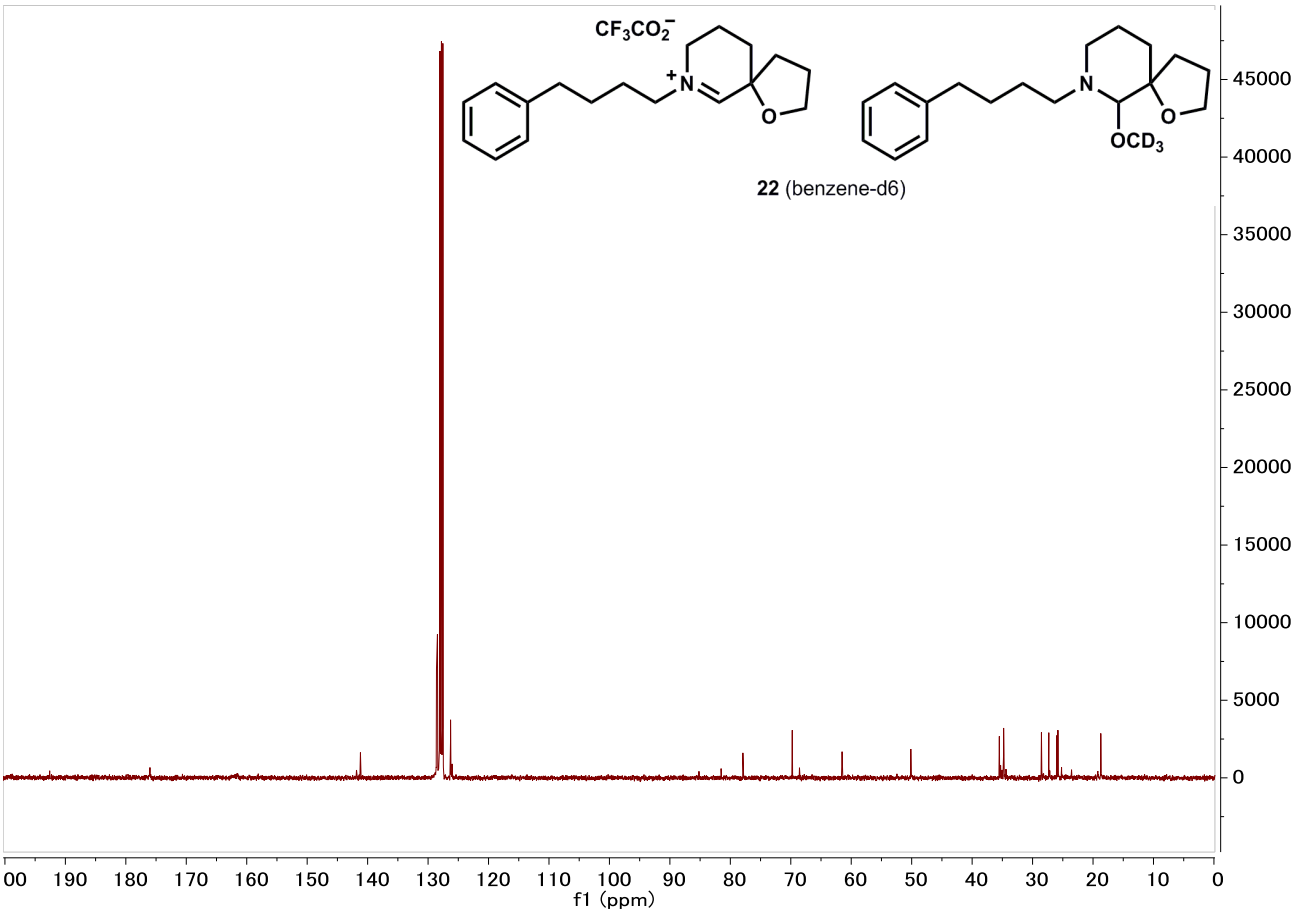

CF3CO2−
F3C
+N
S
21a (13C NMR: THF-d8)
without PhSH
with PhSH (99 equiv)
with PhSH (99 equiv)
3 days after in NMR tube
3
2
1
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

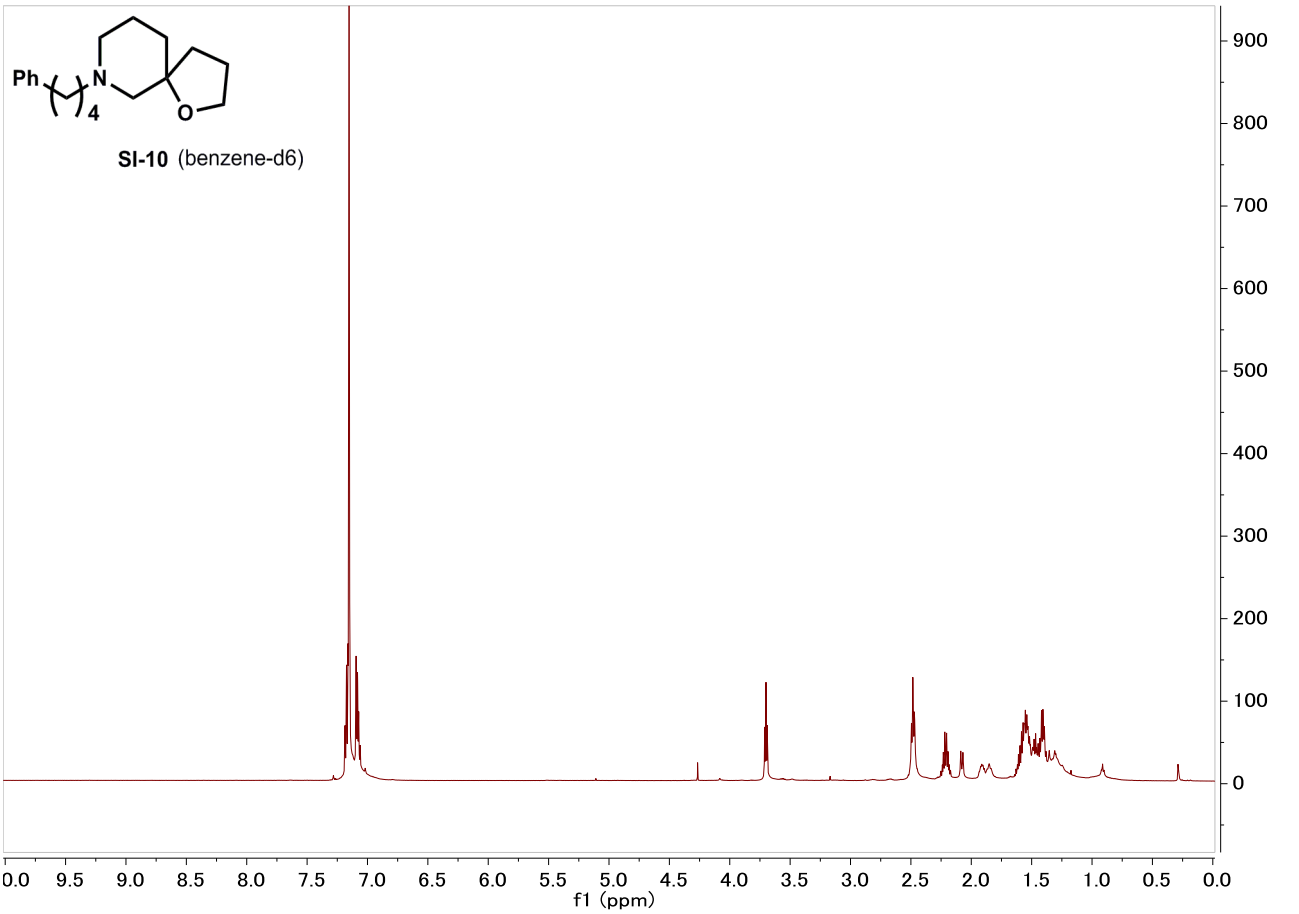

CF3CO2−
F3C
+N
S
21a (HSQC: THF-d8)
with PhSH (99 equiv)
3 days after in NMR tube
f1 (ppm)
f2 (ppm)

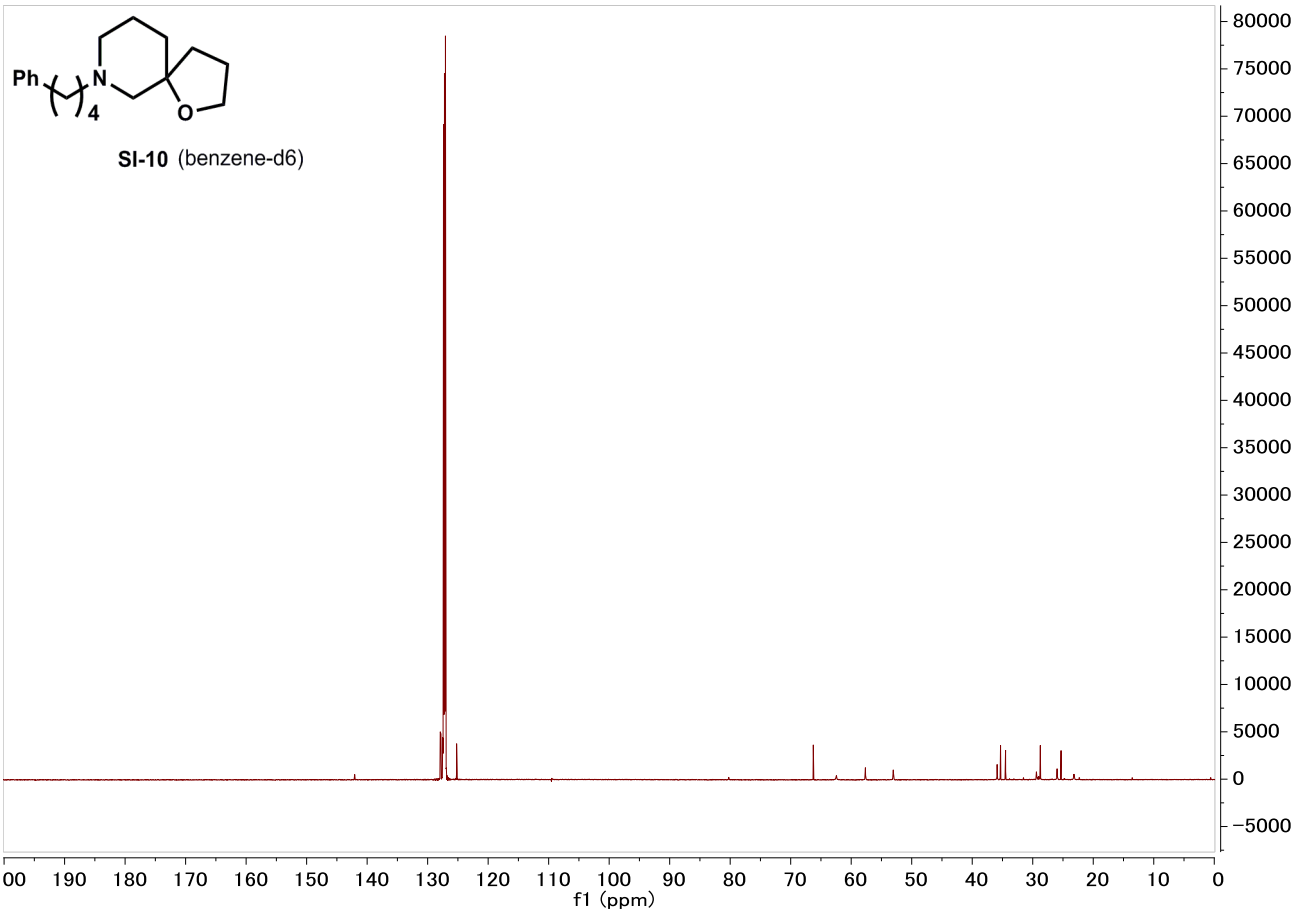

CF3CO2−
+N
O
N
O
OCD3
22 (CD3OD)
f1 (ppm)

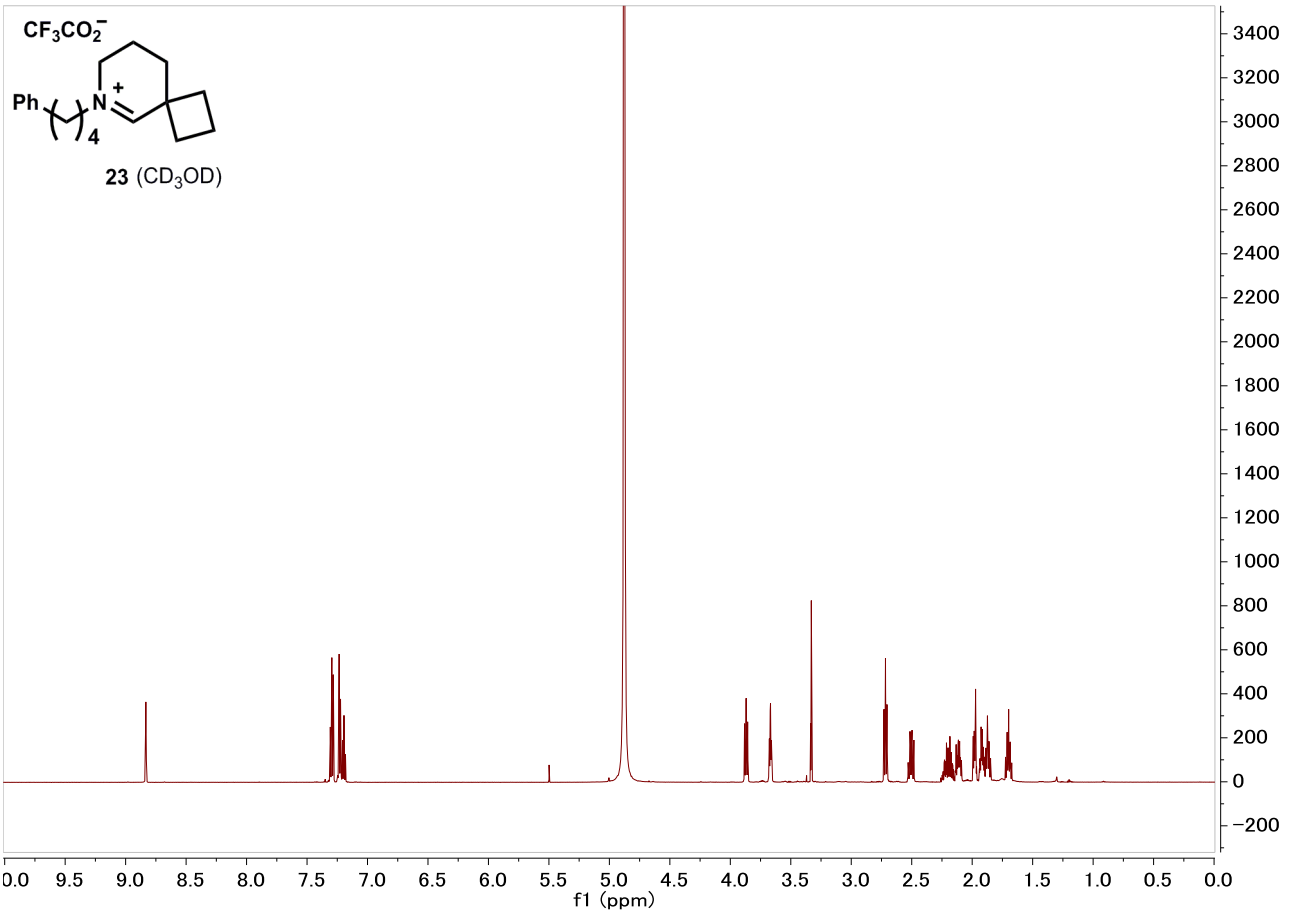

CF3CO2−
+N
O
N
O
OCD3
22 (CD3OD)
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
−5000
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

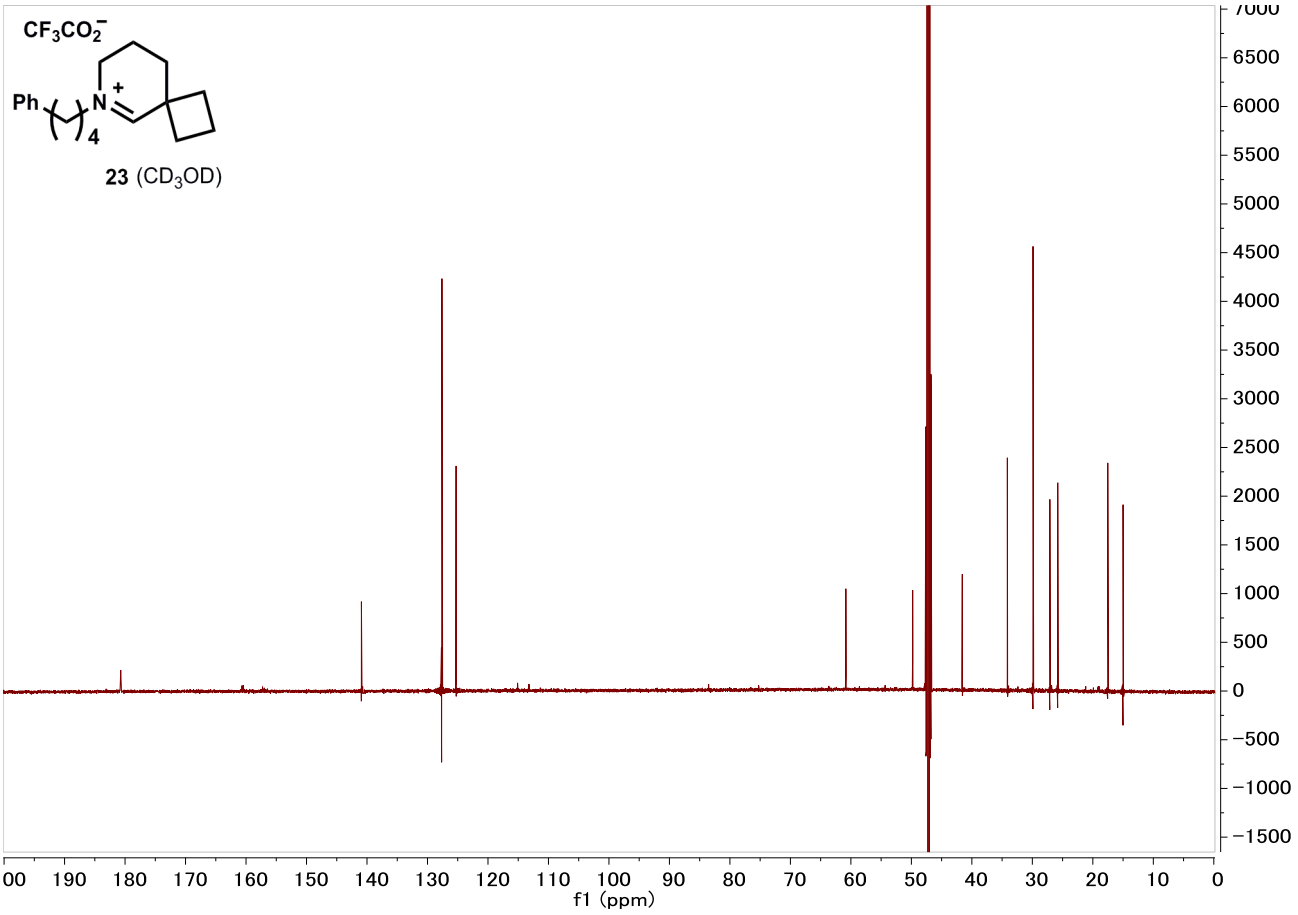

CF3CO2−
+N
O
N
O
OCD3
22 (benzene-d6)
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
−20
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

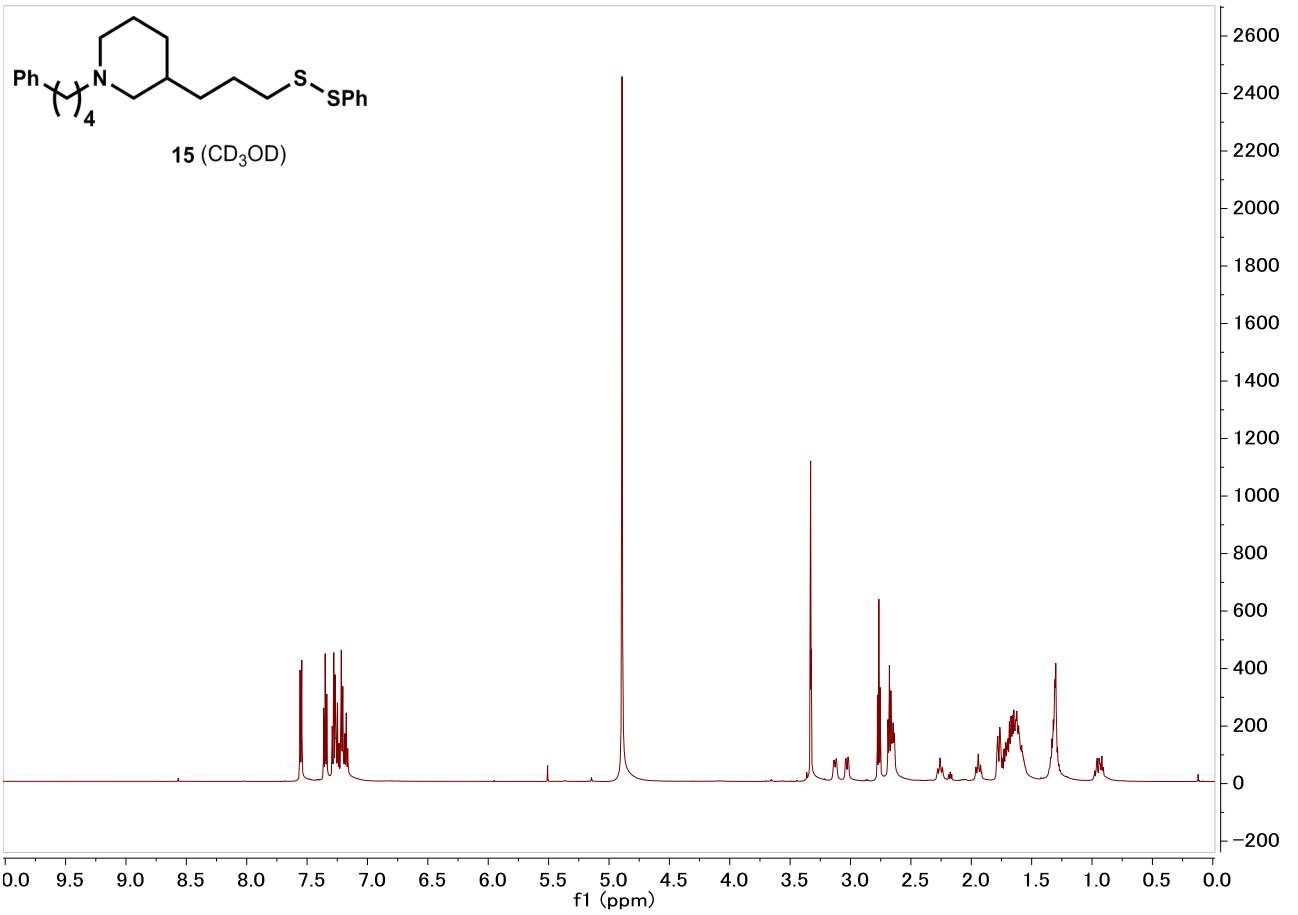

CF3CO2−
+N
O
N
O
OCD3
22 (benzene-d6)
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

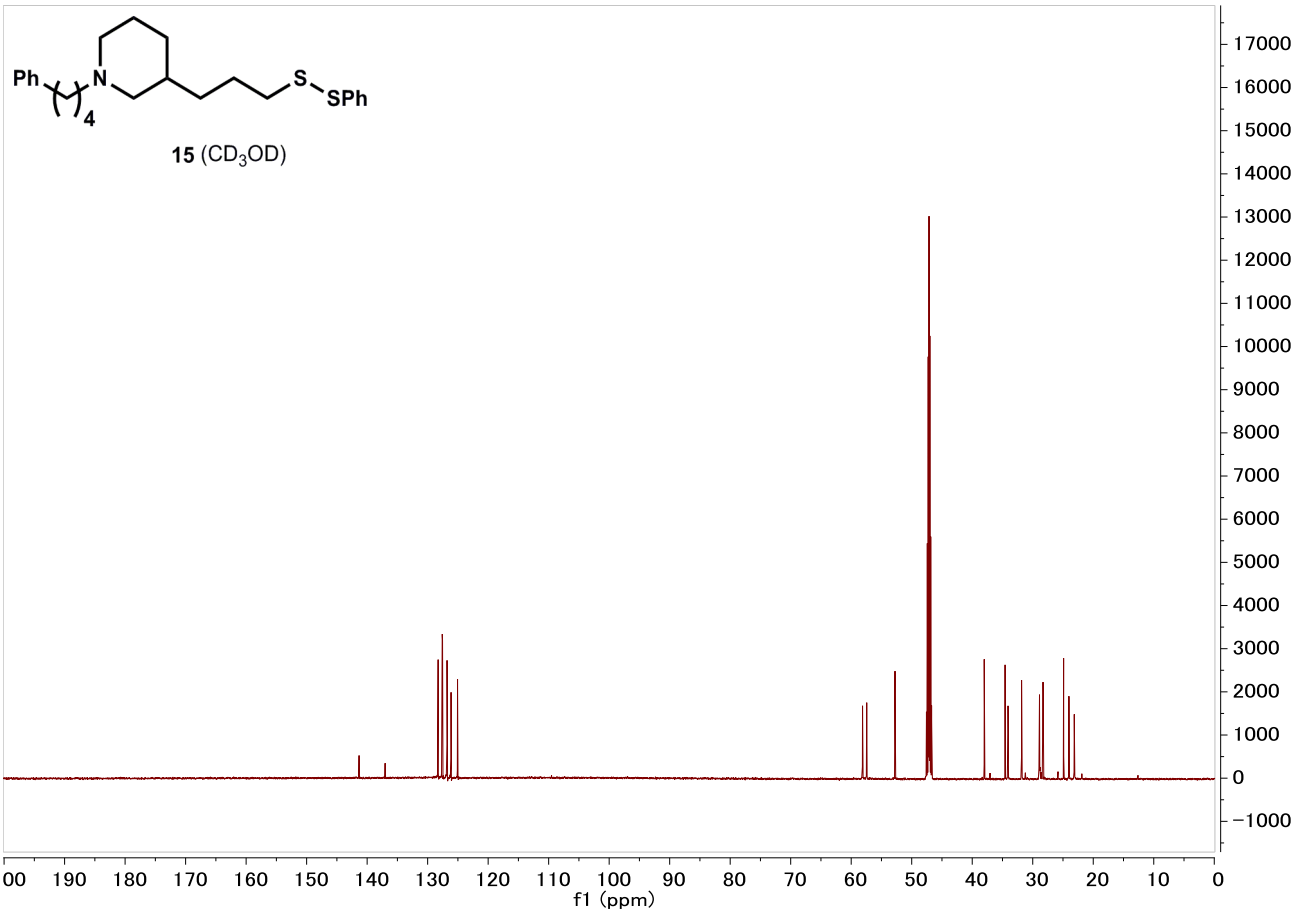

Ph
N
4
O
SI-10 (benzene-d6)
900
800
700
600
500
400
300
200
100
0
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

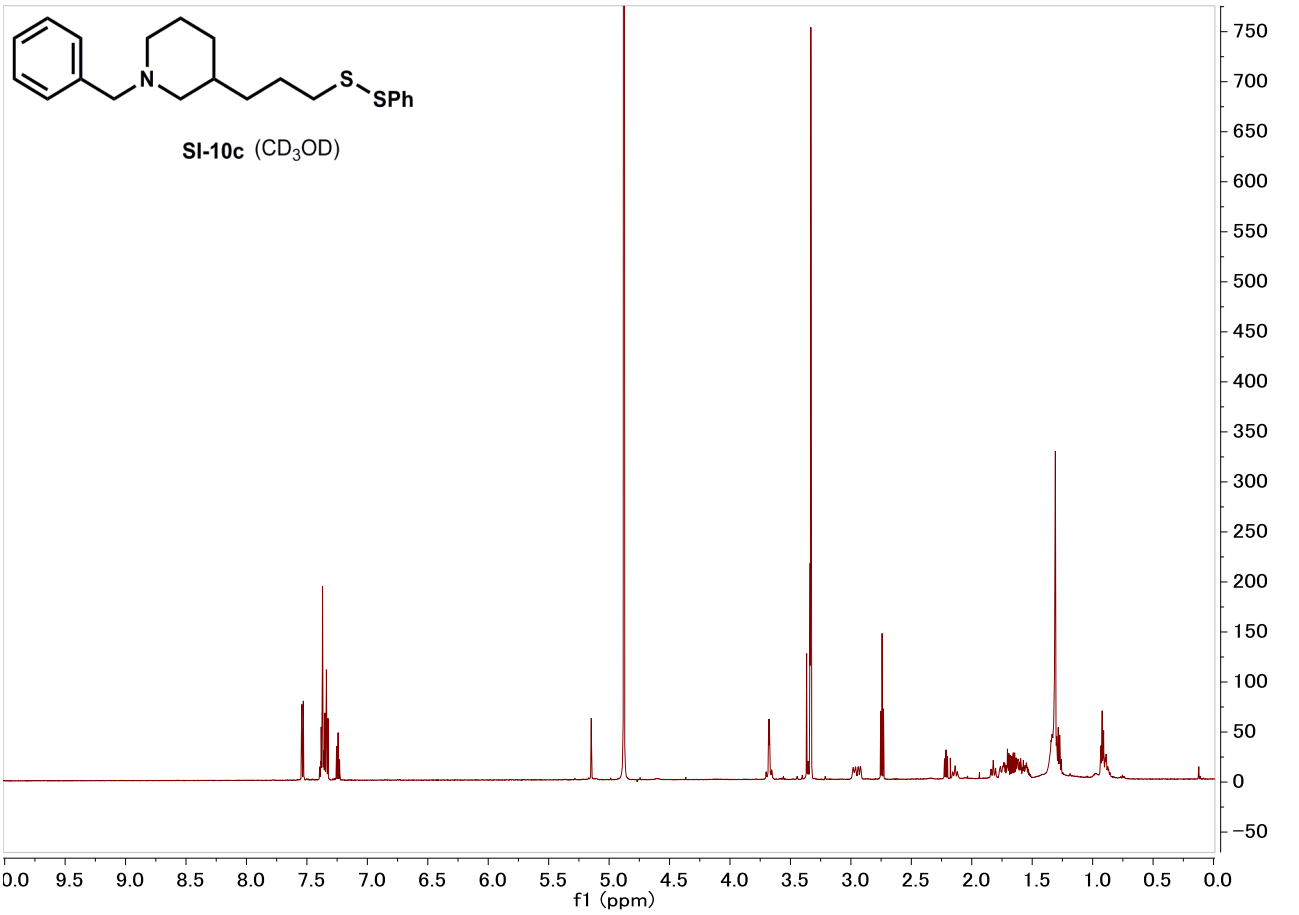

Ph
N
4
O
SI-10 (benzene-d6)
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
−5000
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

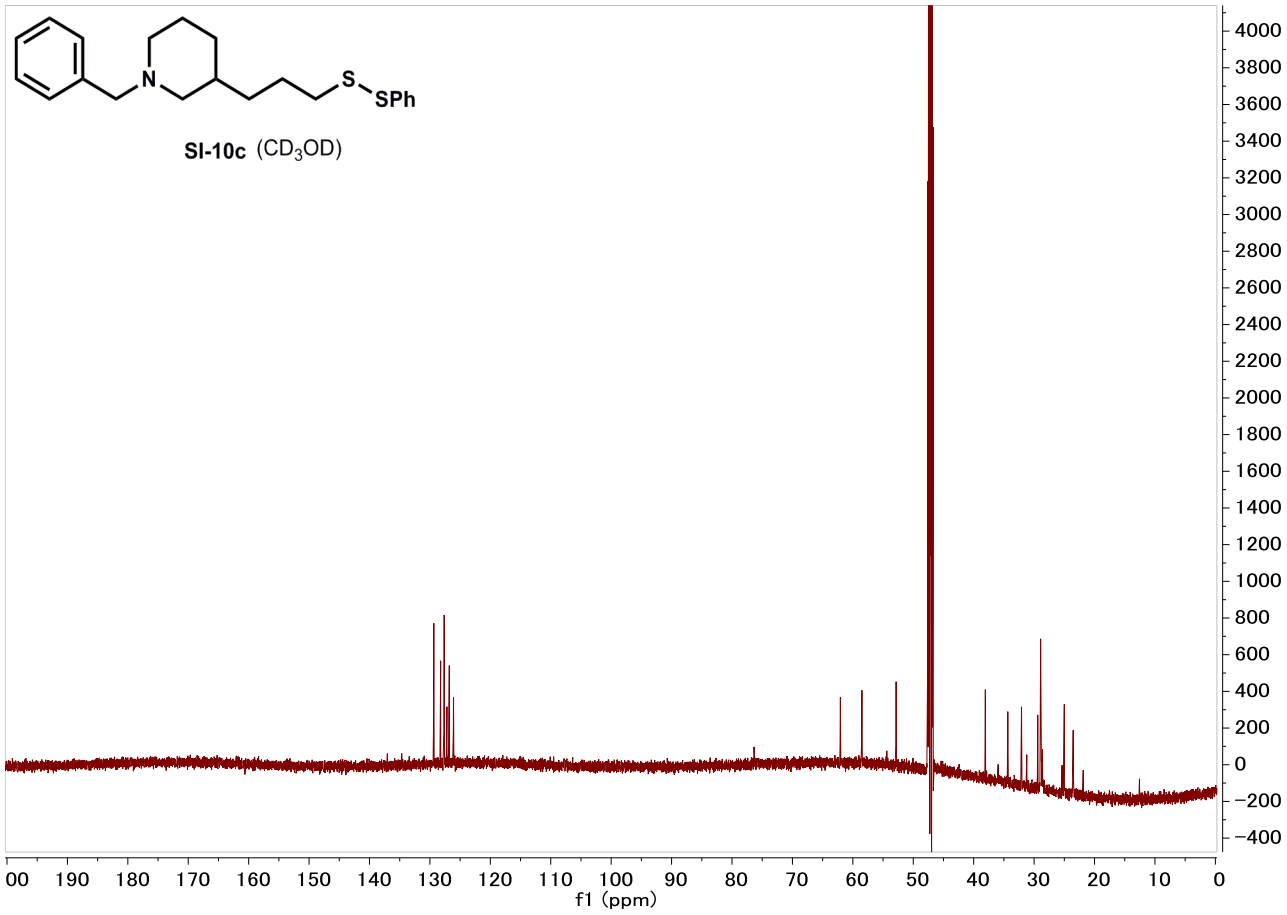

CF3CO2−
Ph
N+
4
23 (CD3OD)
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

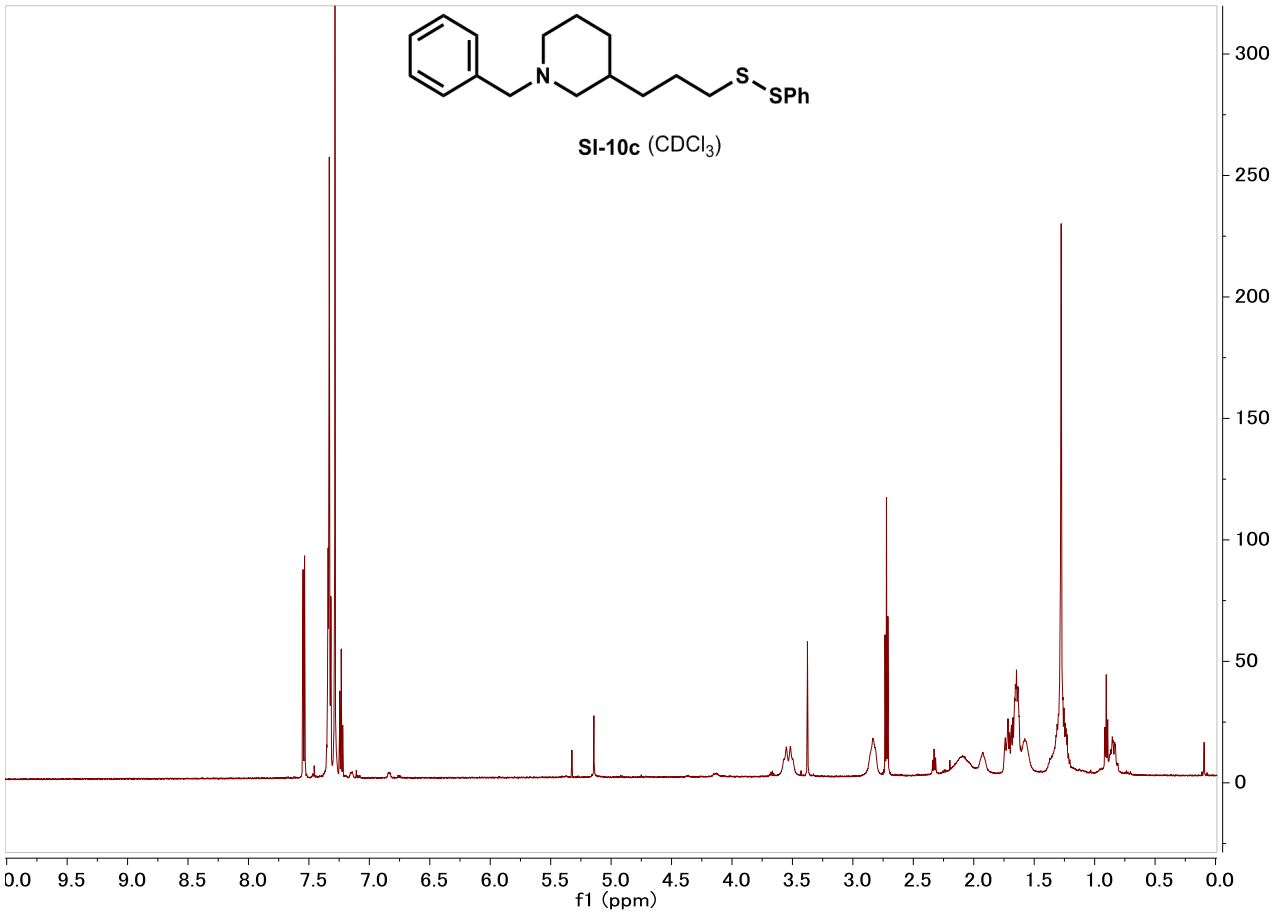

CF3CO2−
Ph
N
+
4
23 (CD3OD)
f1 (ppm)

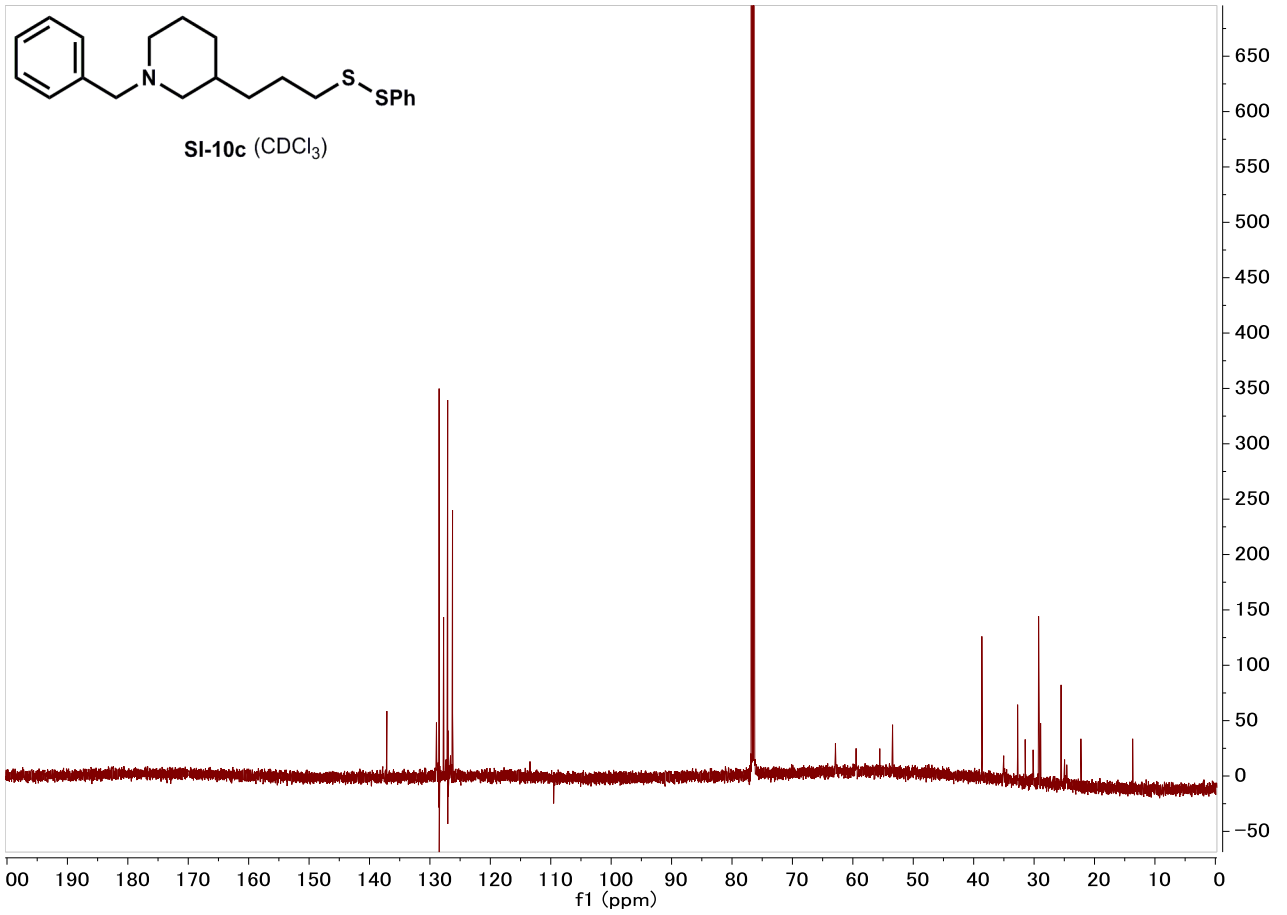

Ph
N
S
SPh
4
15 (CD3OD)
f1 (ppm)

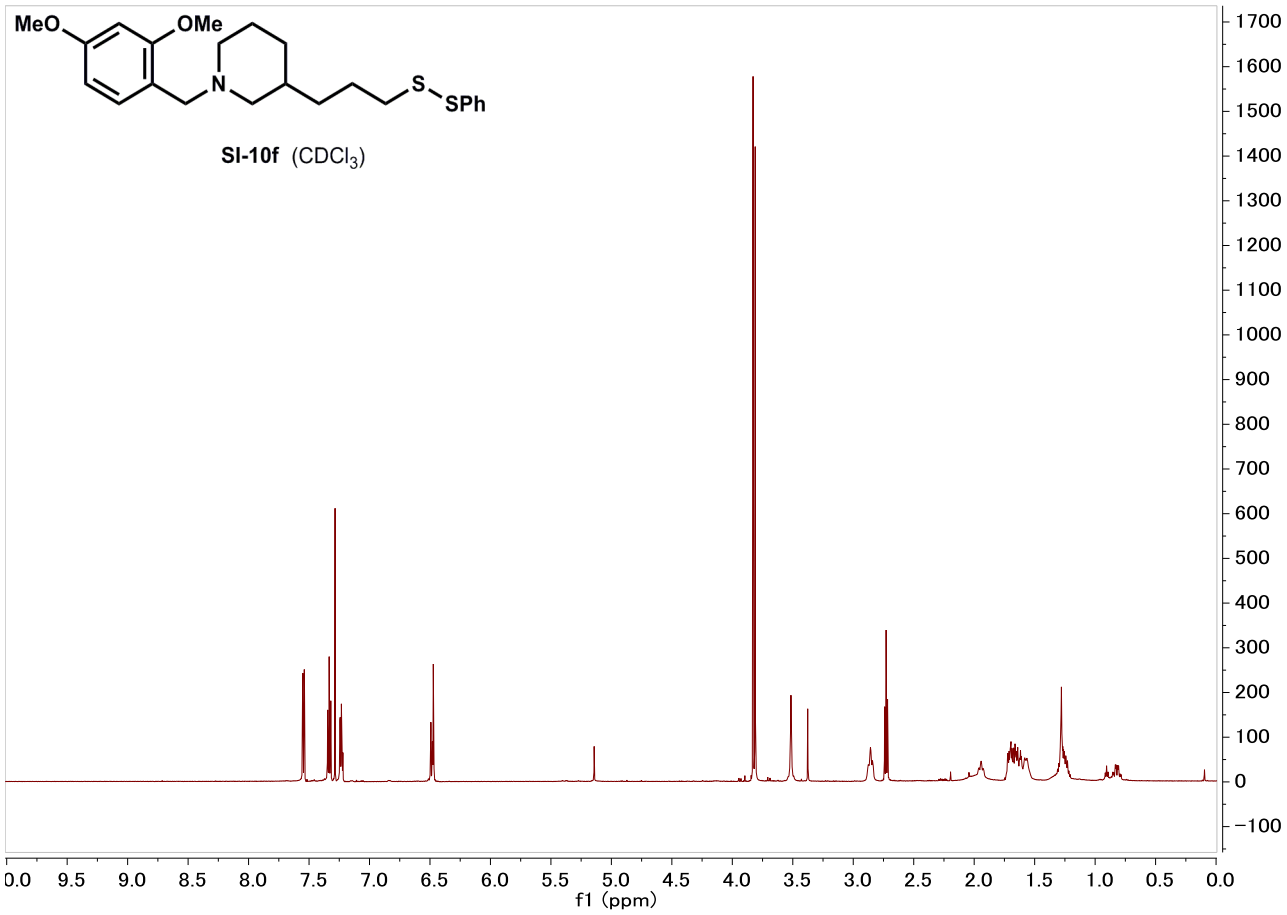

Ph
N
4
S
SPh
15 (CD3OD)
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

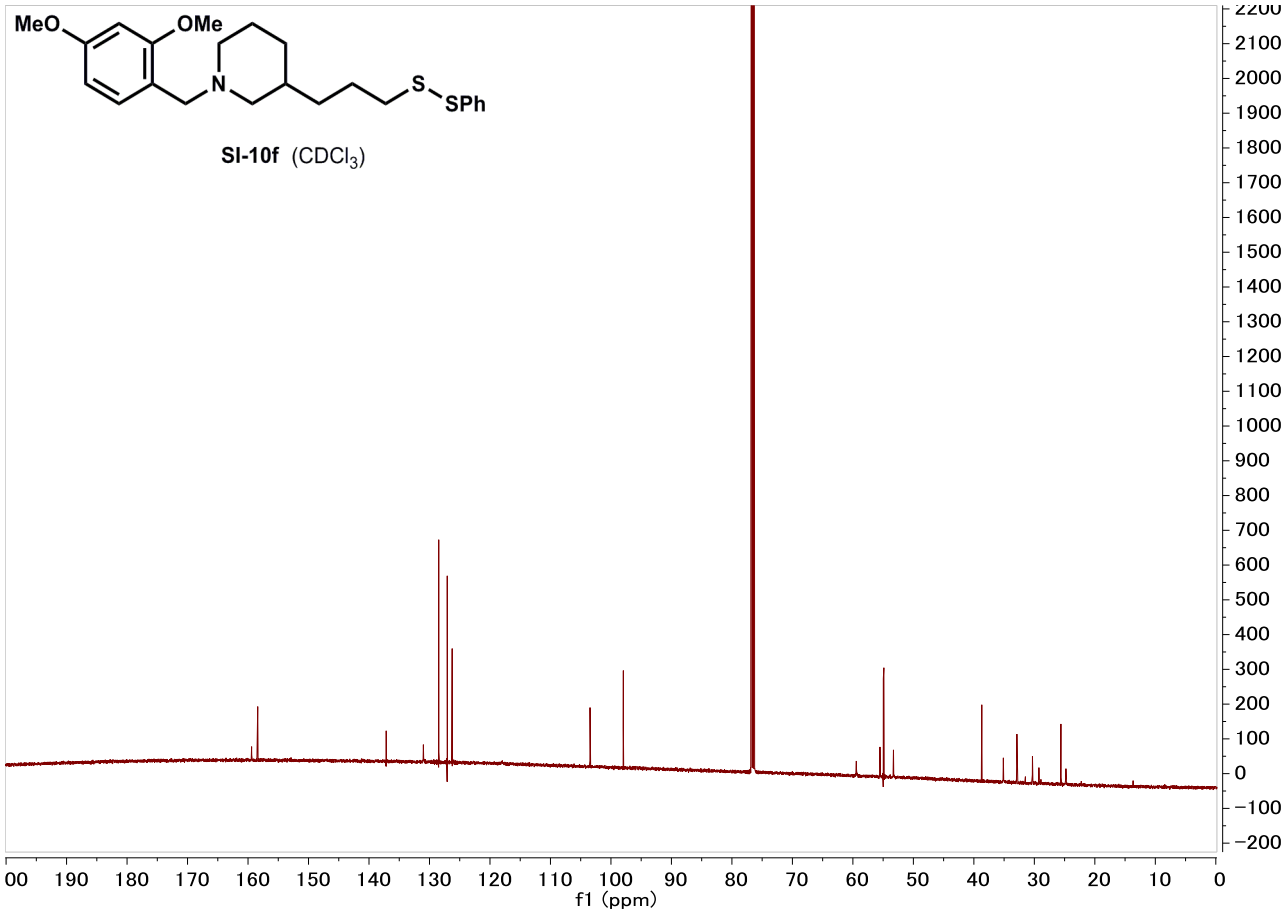

N
S
SPh
SI-10c (CD3OD)
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
−50
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

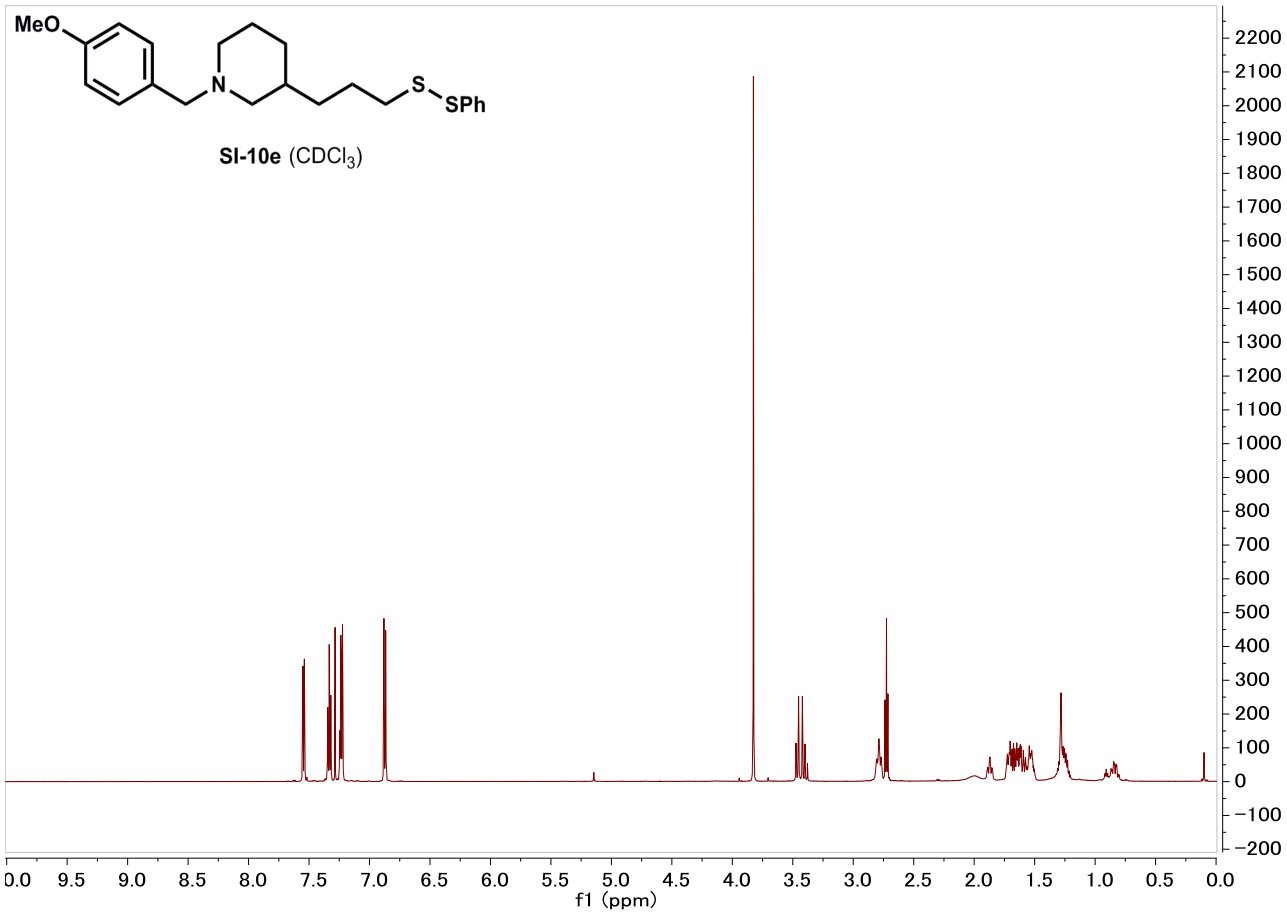

N
S
SPh
SI-10c (CD3OD)
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
−400
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

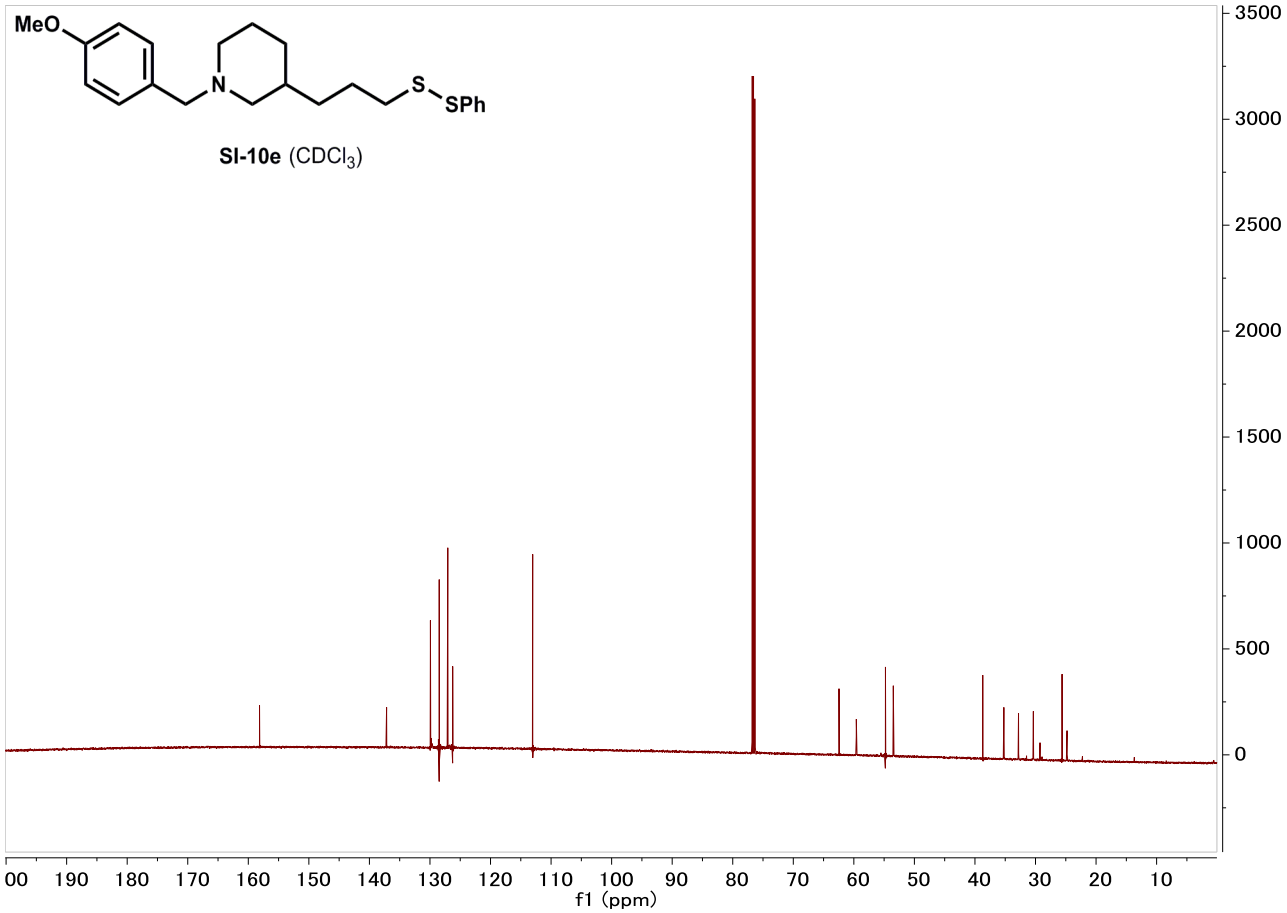

N
S
SPh
SI-10c (CDCl3)
300
250
200
150
100
50
0
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

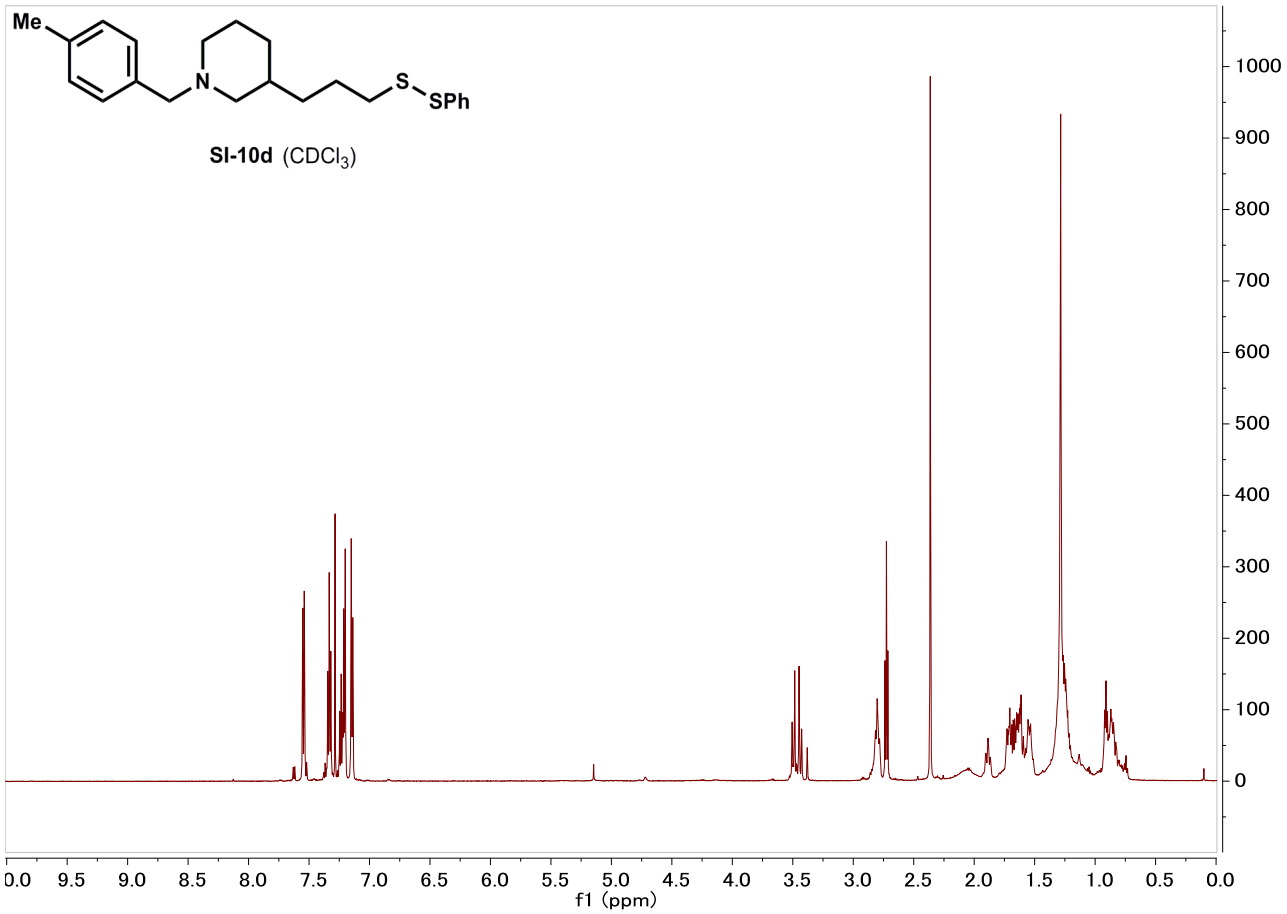

N
S
SPh
SI-10c (CDCl3)
650
600
550
500
450
400
350
300
250
200
150
100
50
0
−50
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

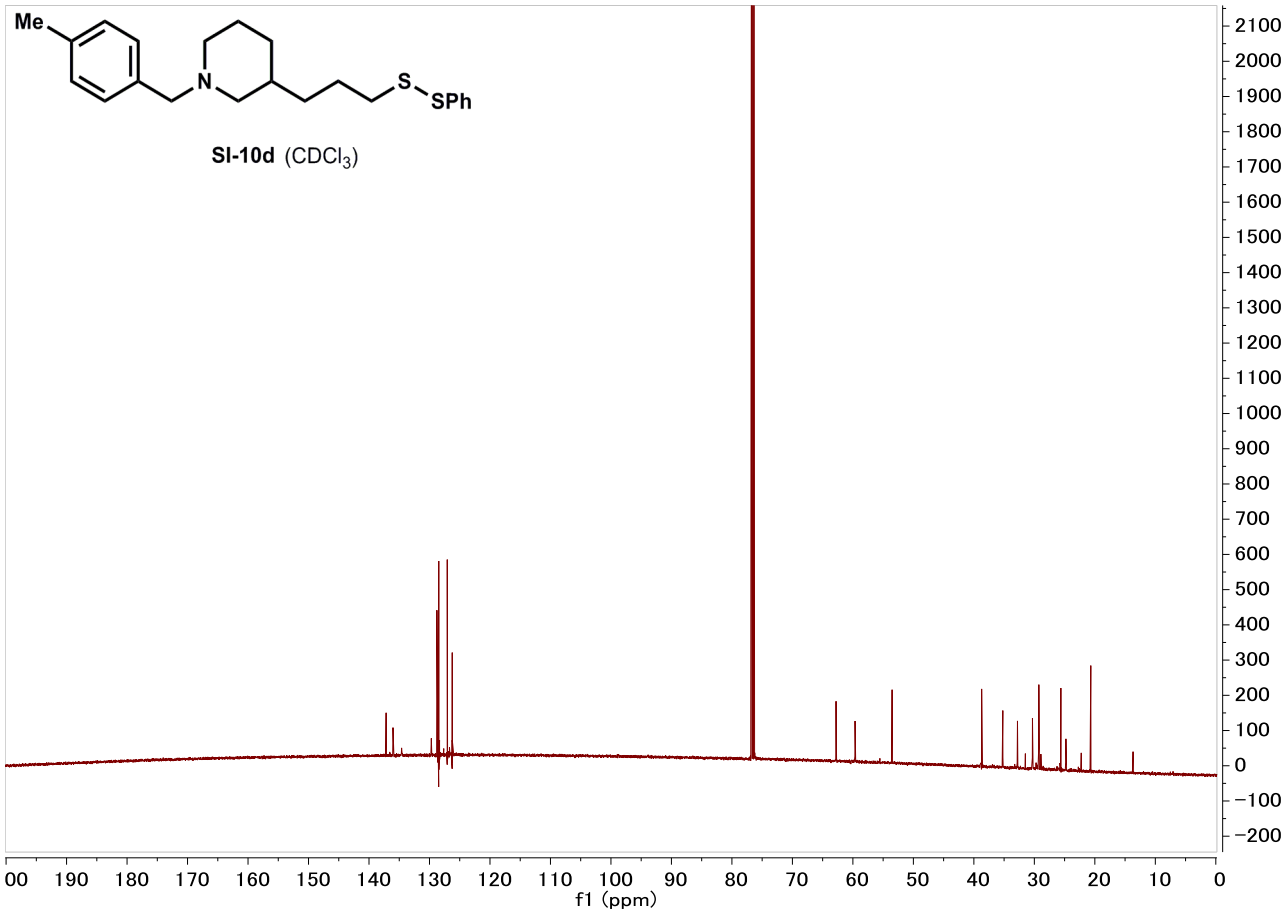

MeO
OMe
N
S
SPh
SI-10f (CDCl3)
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

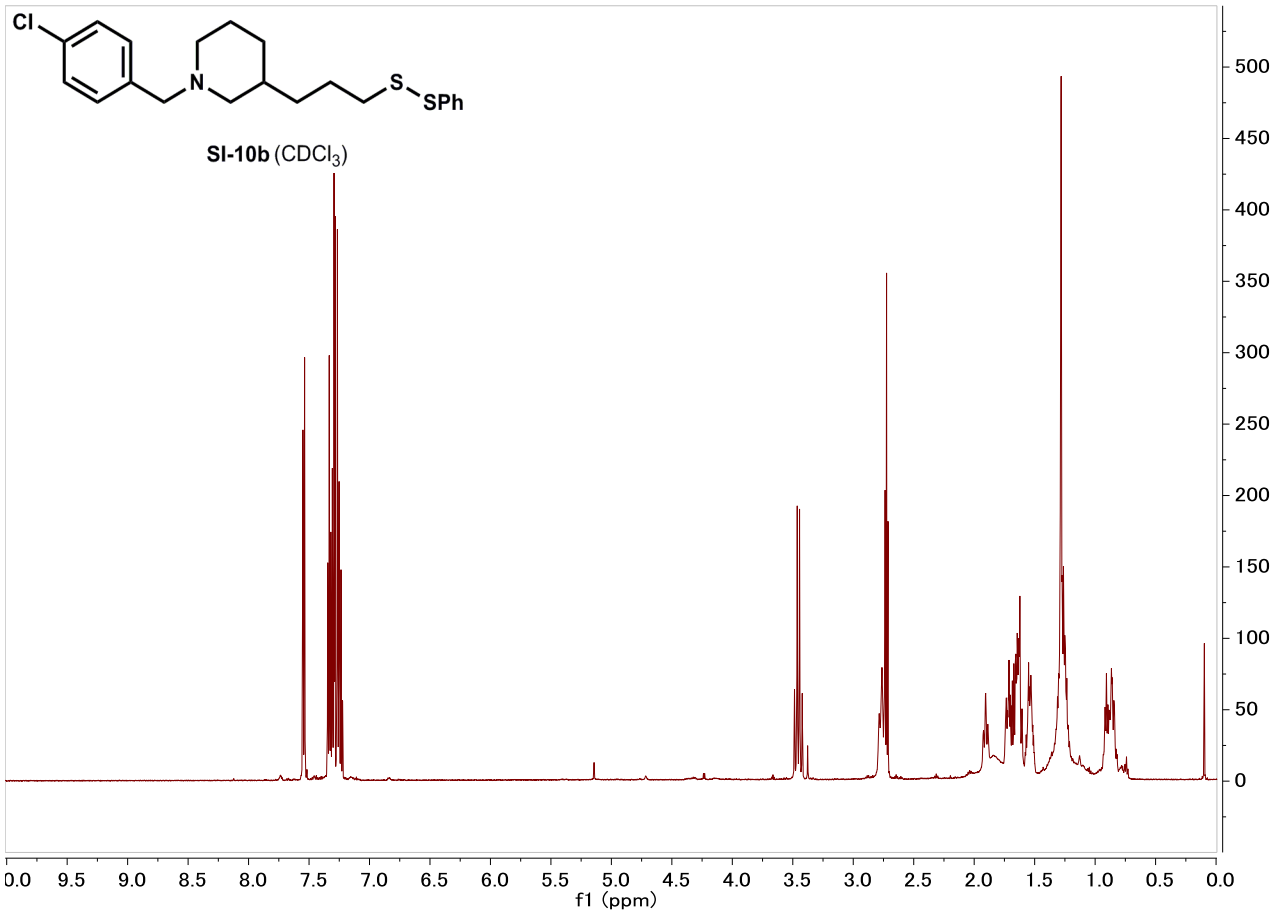

MeO
OMe
N
S
SPh
SI-10f (CDCl3)
f1 (ppm)

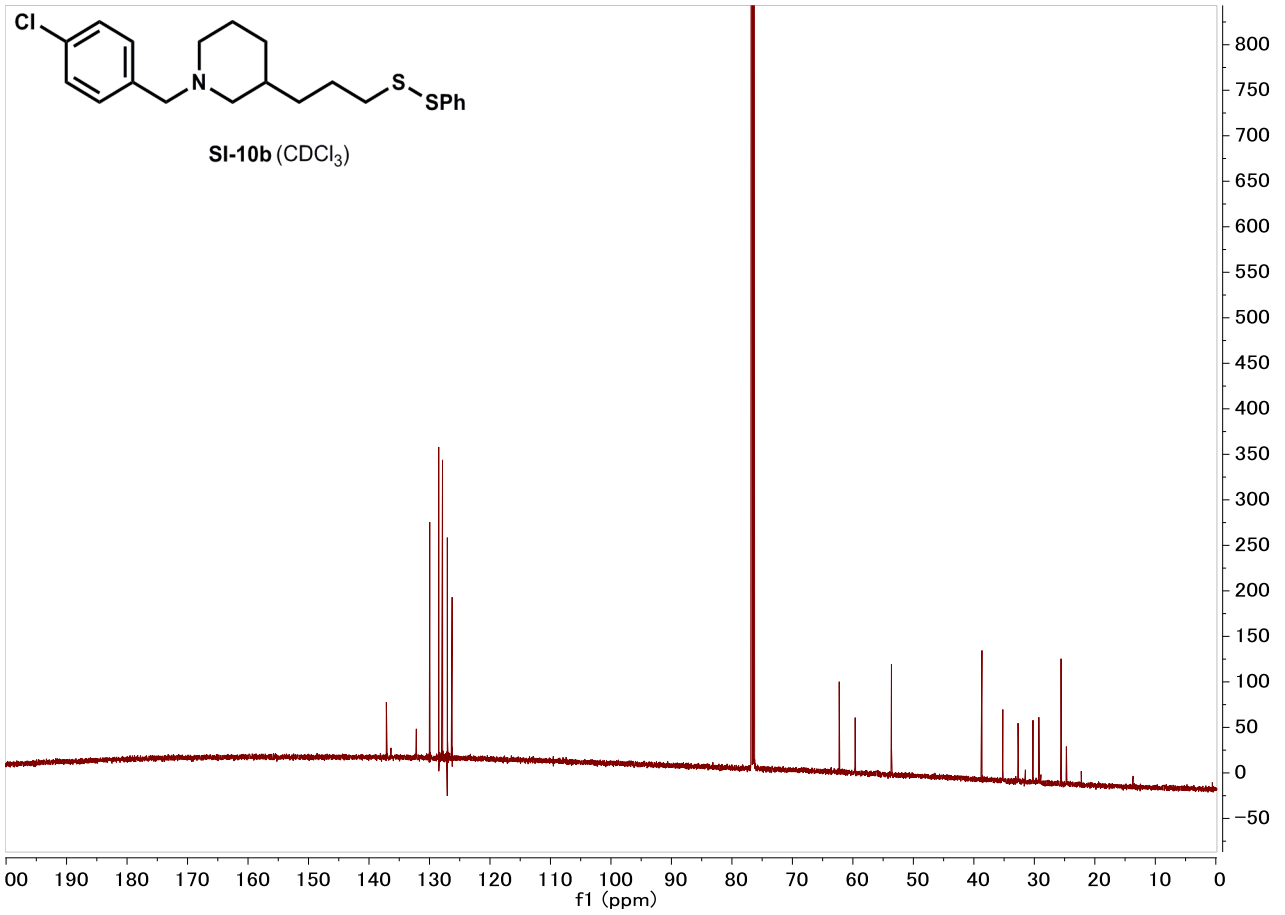

MeO
N
S
SPh
SI-10e (CDCl3)
f1 (ppm)


MeO
N
S
SPh
SI-10e (CDCl3)
3500
3000
2500
2000
1500
1000
500
0
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

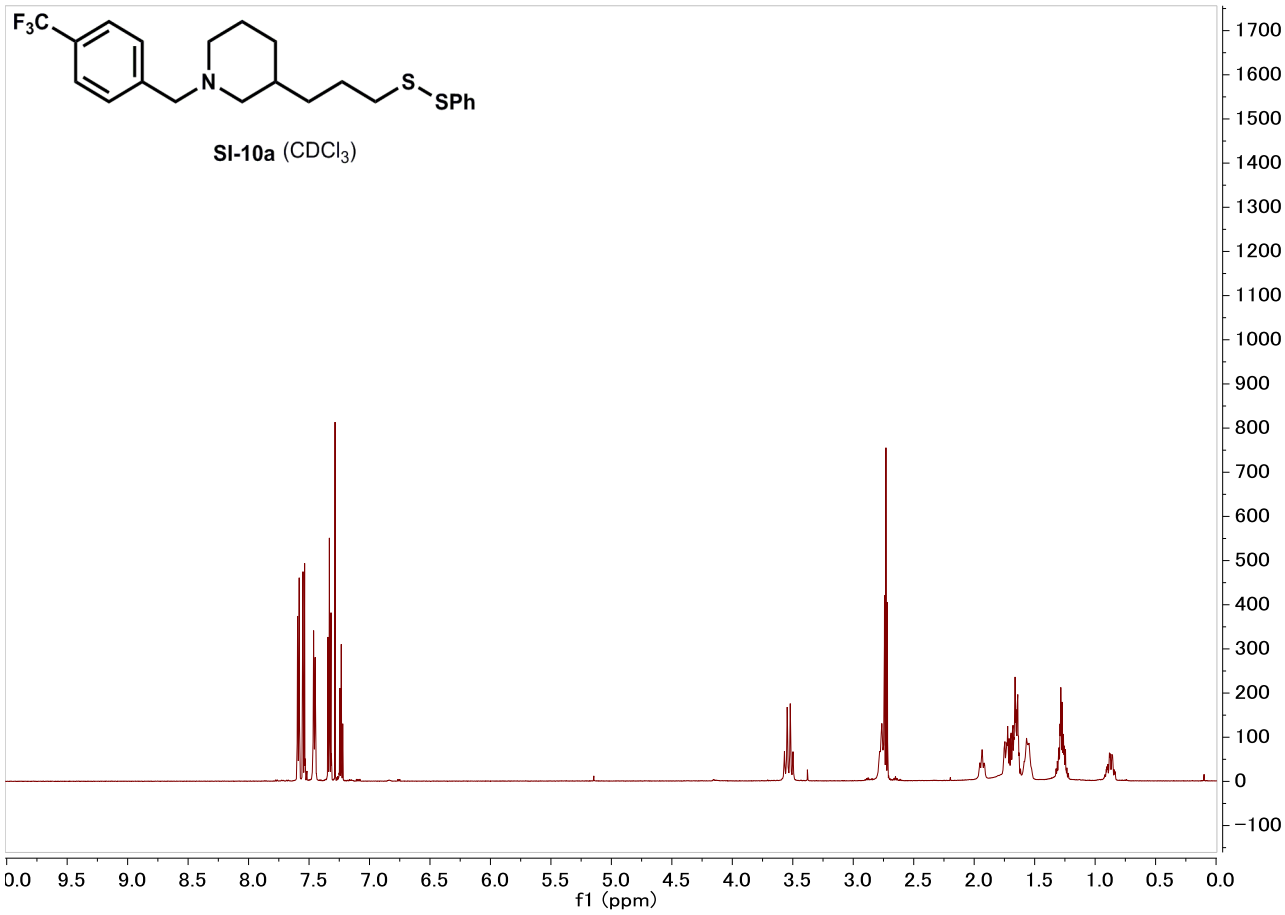

Me
N
S
SPh
SI-10d (CDCl3)
1000
900
800
700
600
500
400
300
200
100
0
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


Me
N
S
SPh
SI-10d (CDCl3)
f1 (ppm)

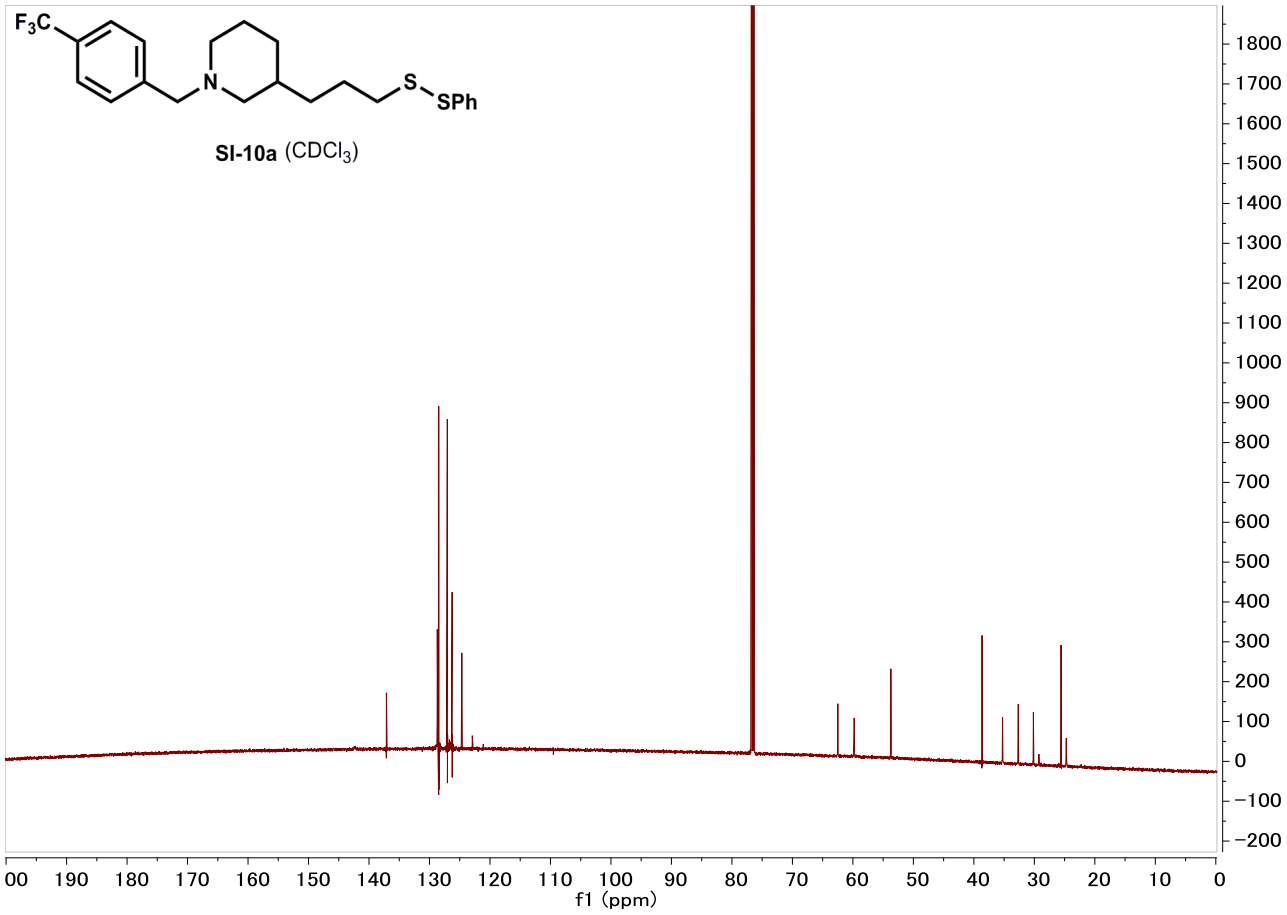

Cl
N
S
SPh
SI-10b (CDCl3)
f1 (ppm)

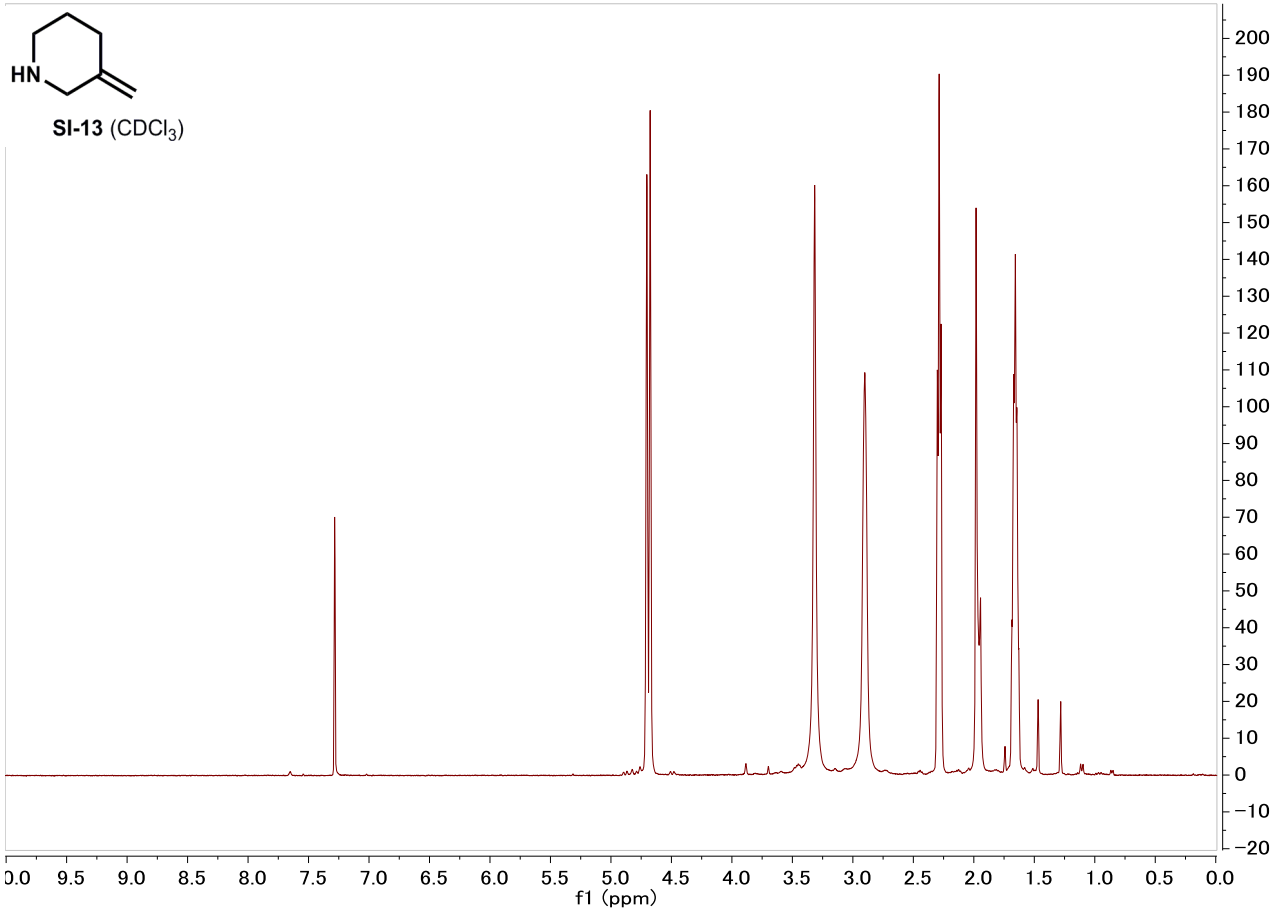


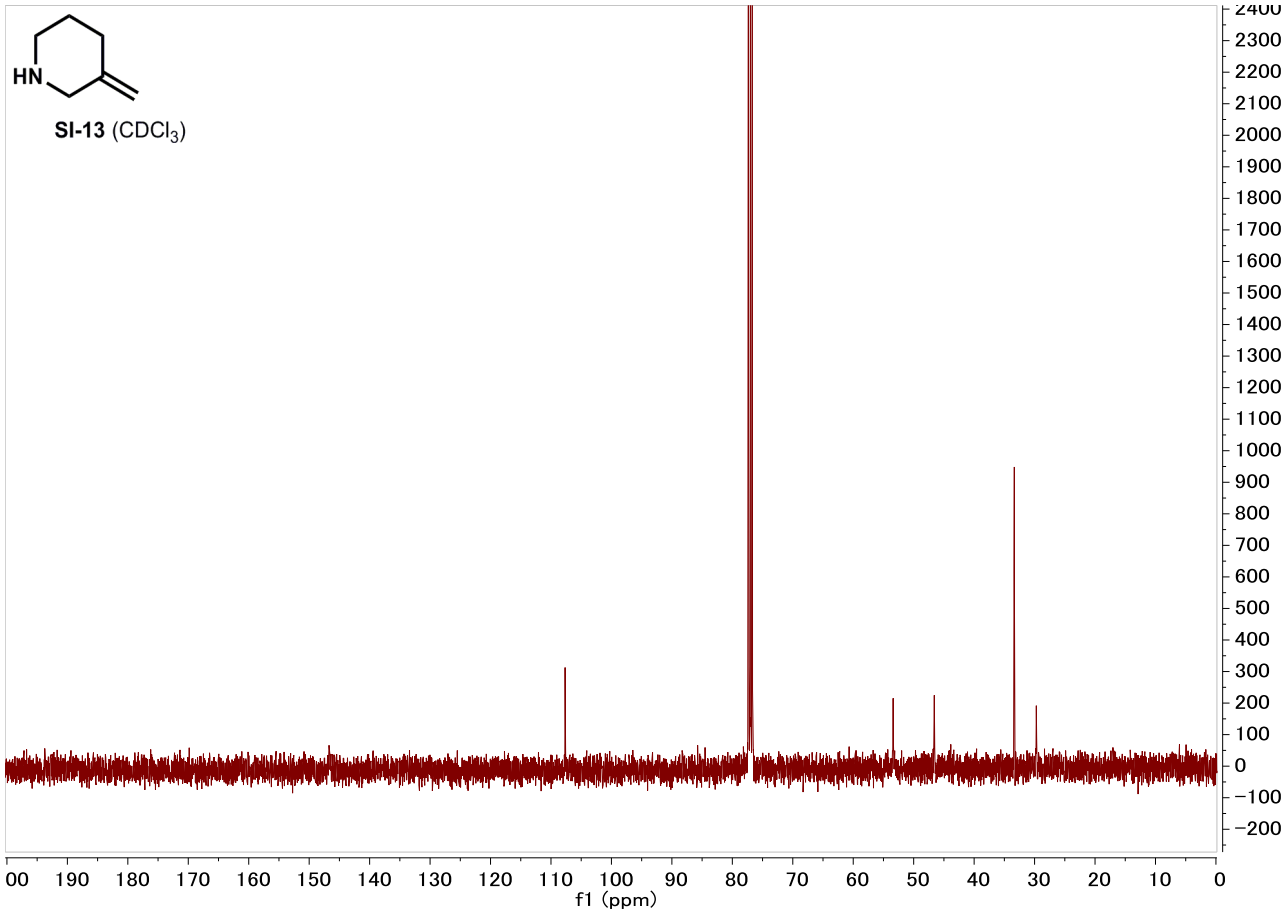
SI-10b ($CDCl_3$)

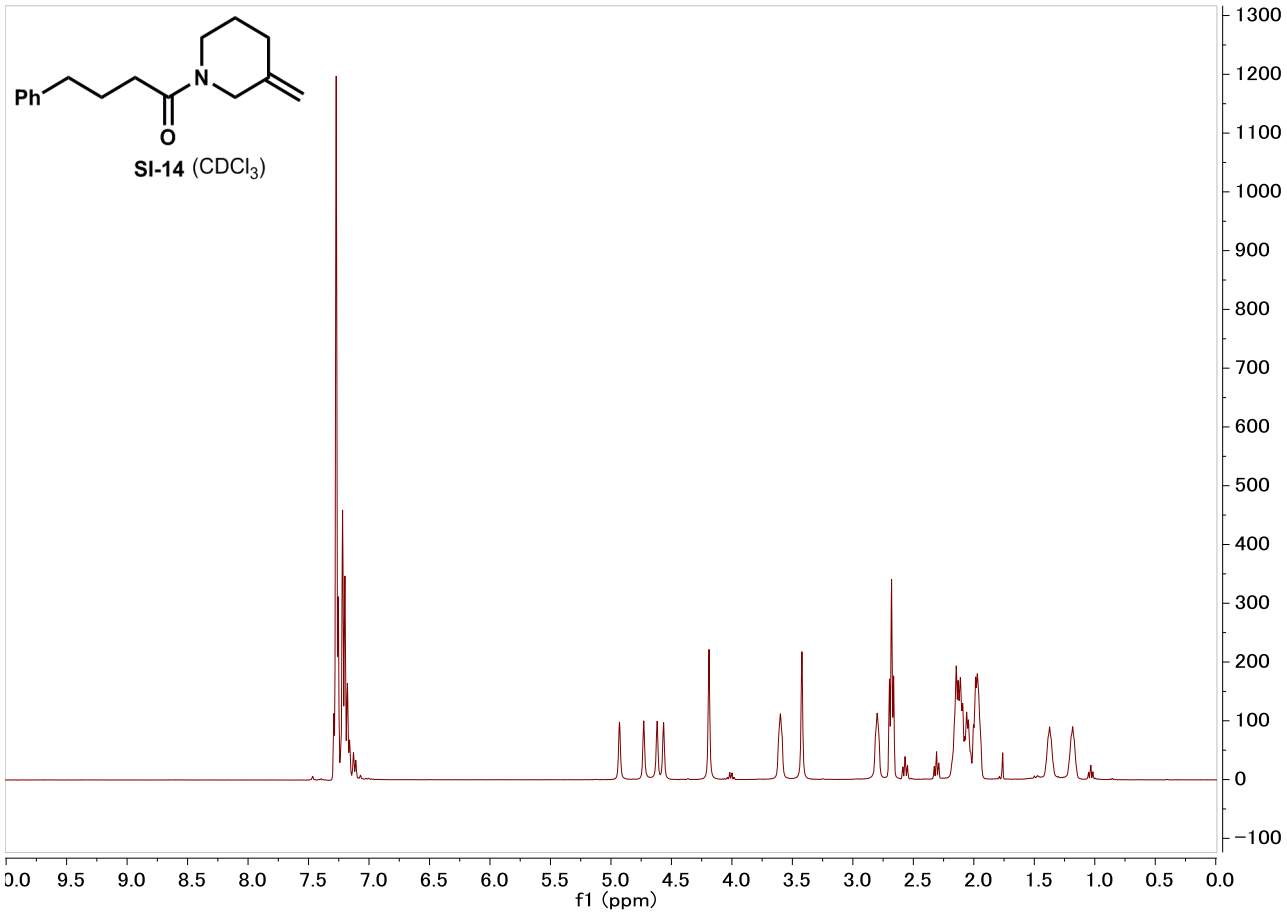


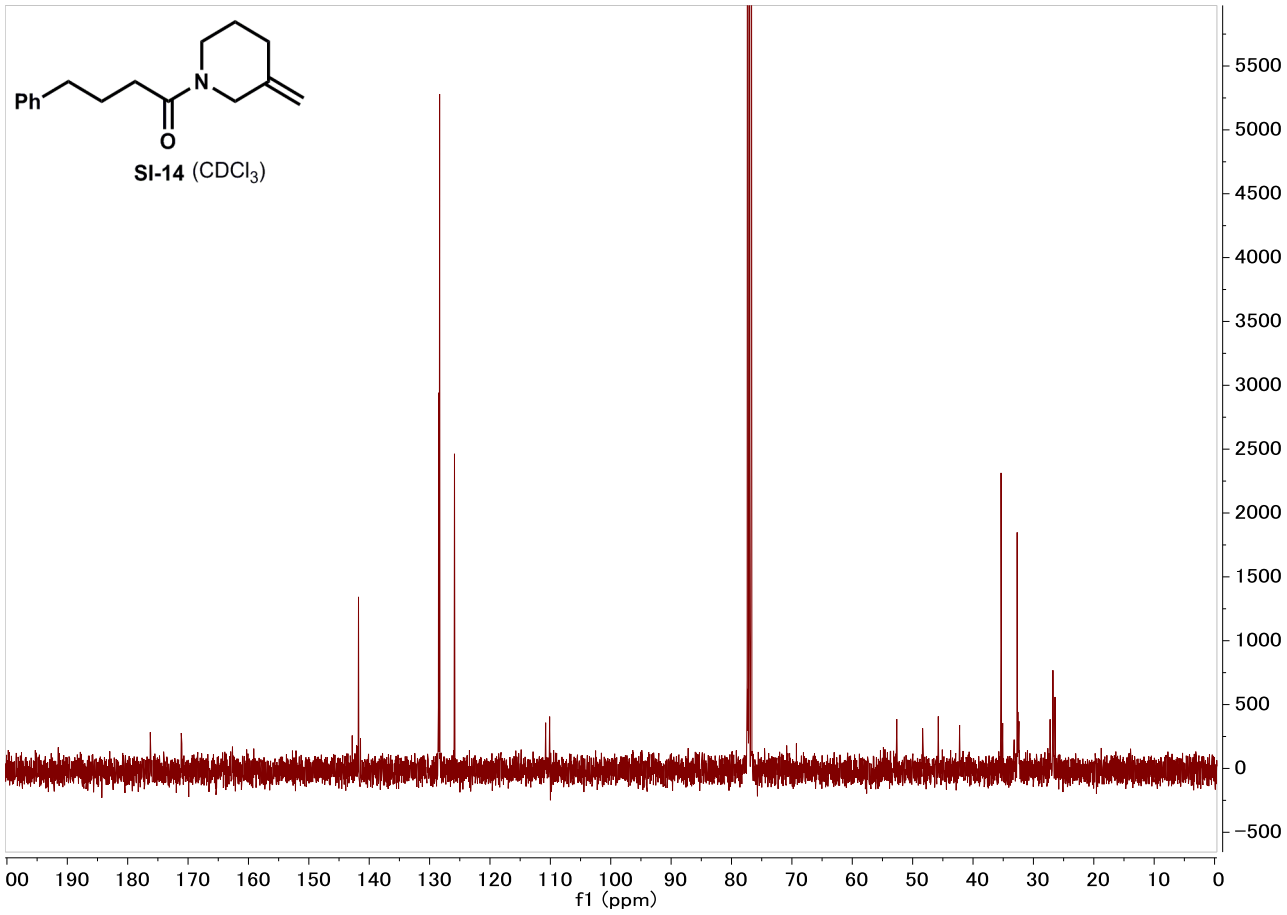
SI-10a ($CDCl_3$)

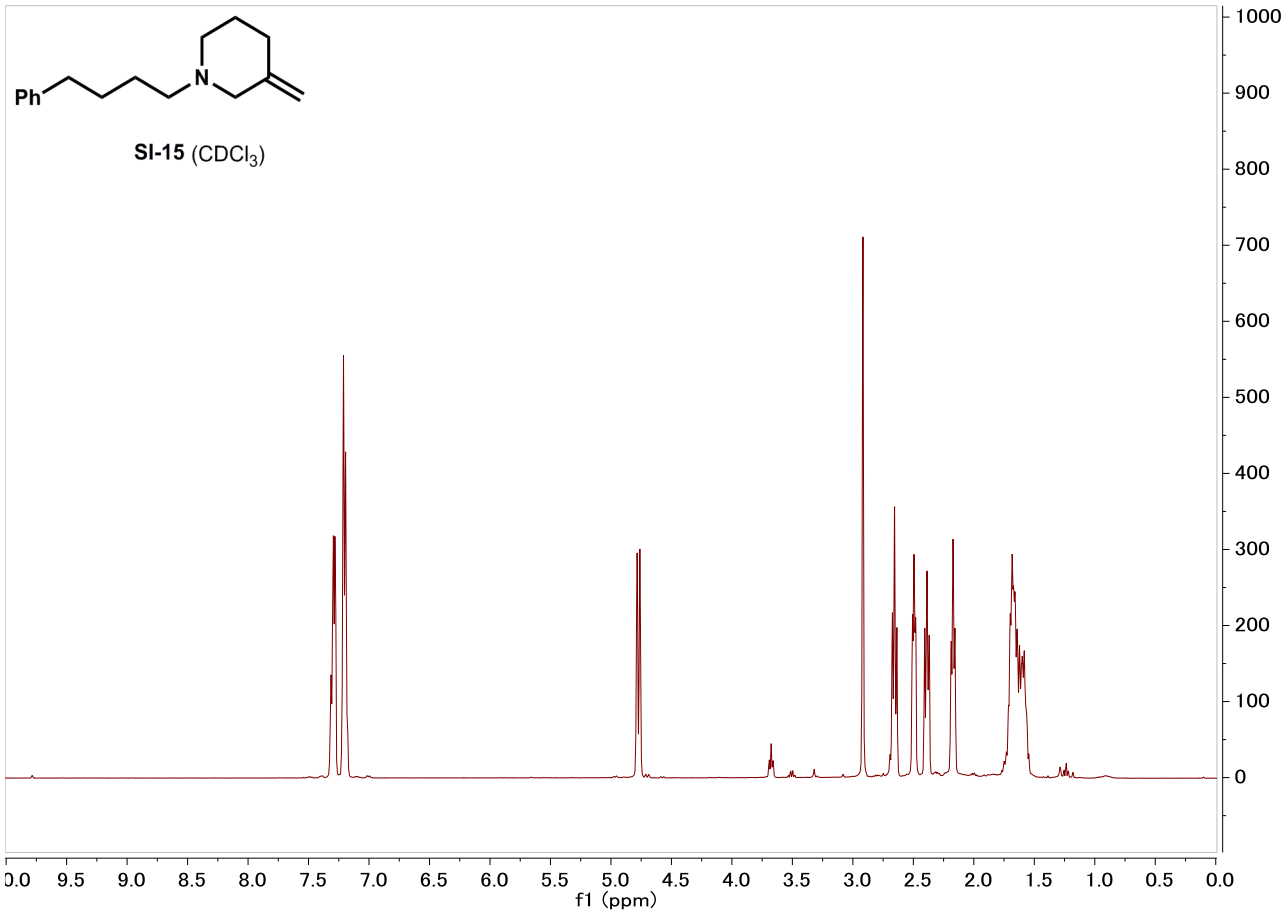

F3C
N
S
SPh
SI-10a (CDCl3)
f1 (ppm)

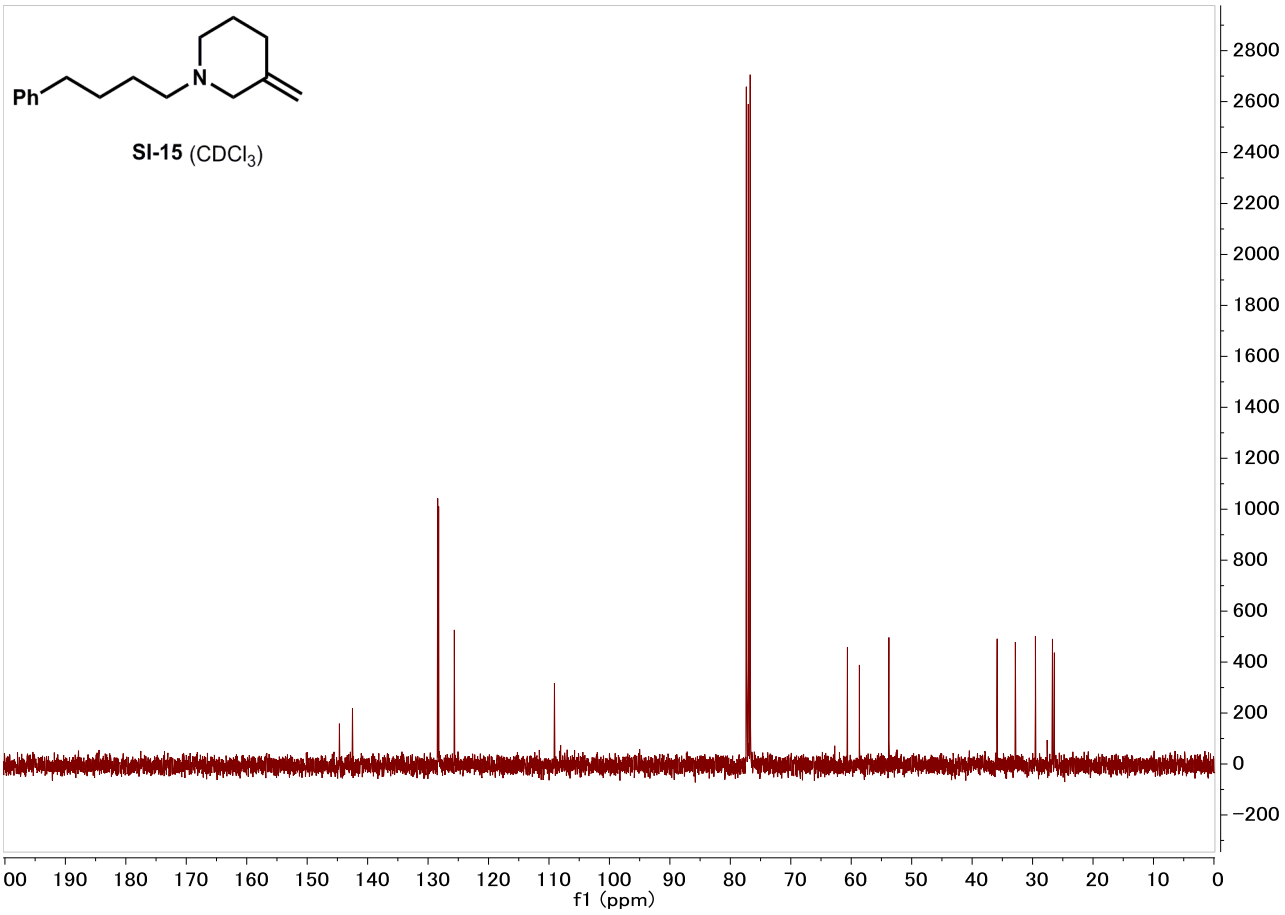

HN
SI-13 (CDCl3)
f1 (ppm)

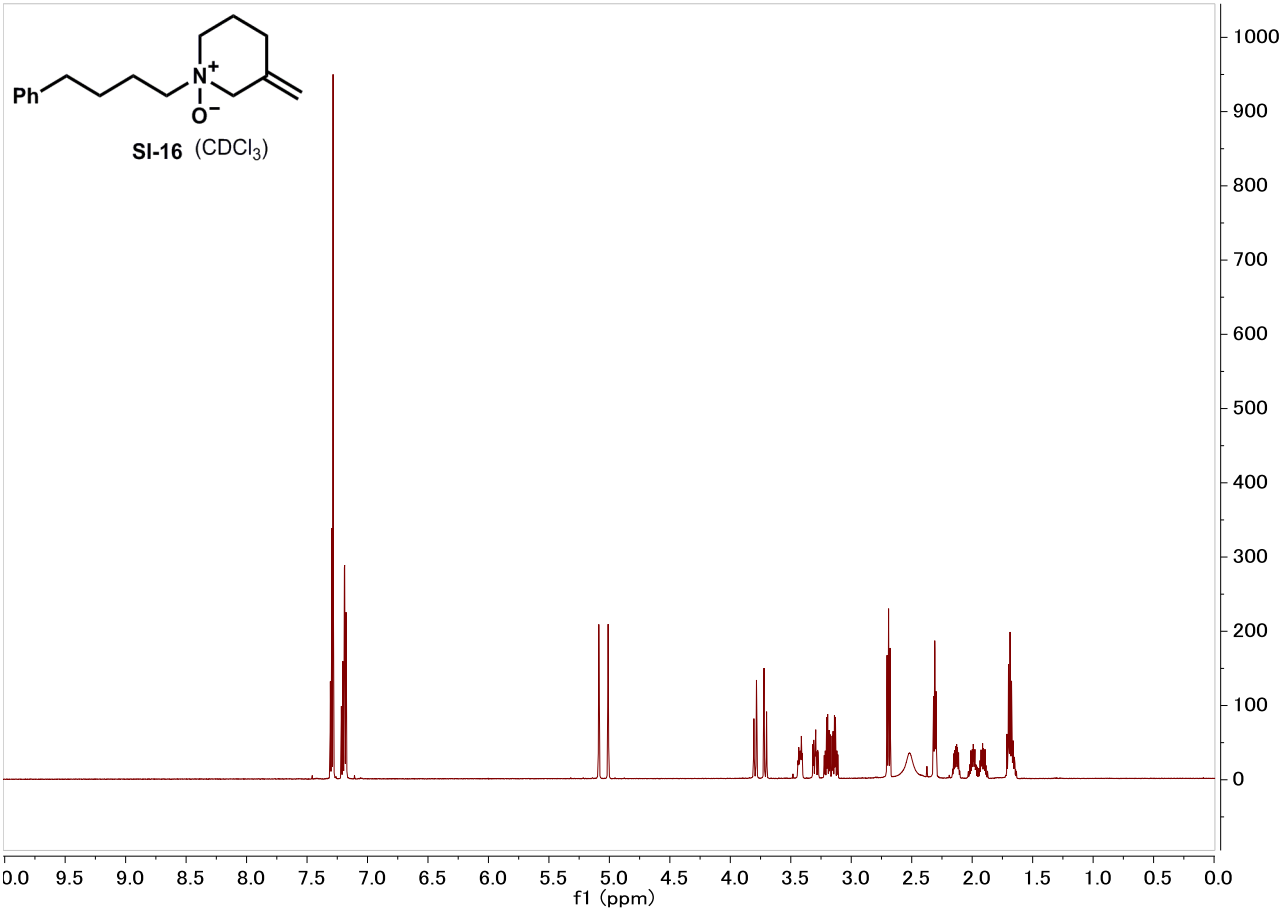

HN
SI-13 (CDCl3)
f1 (ppm)

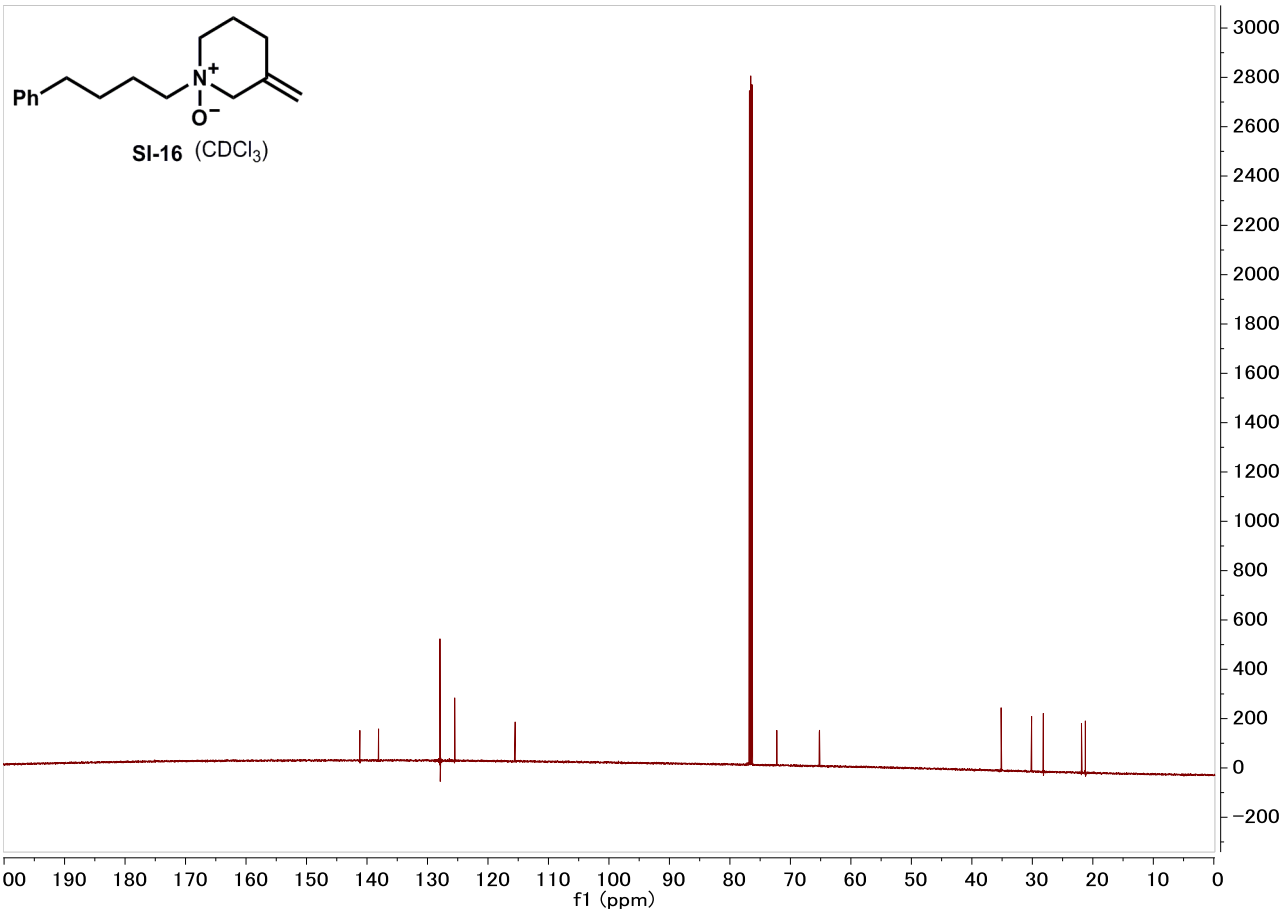

Ph
N
O
SI-14 (CDCl3)
f1 (ppm)

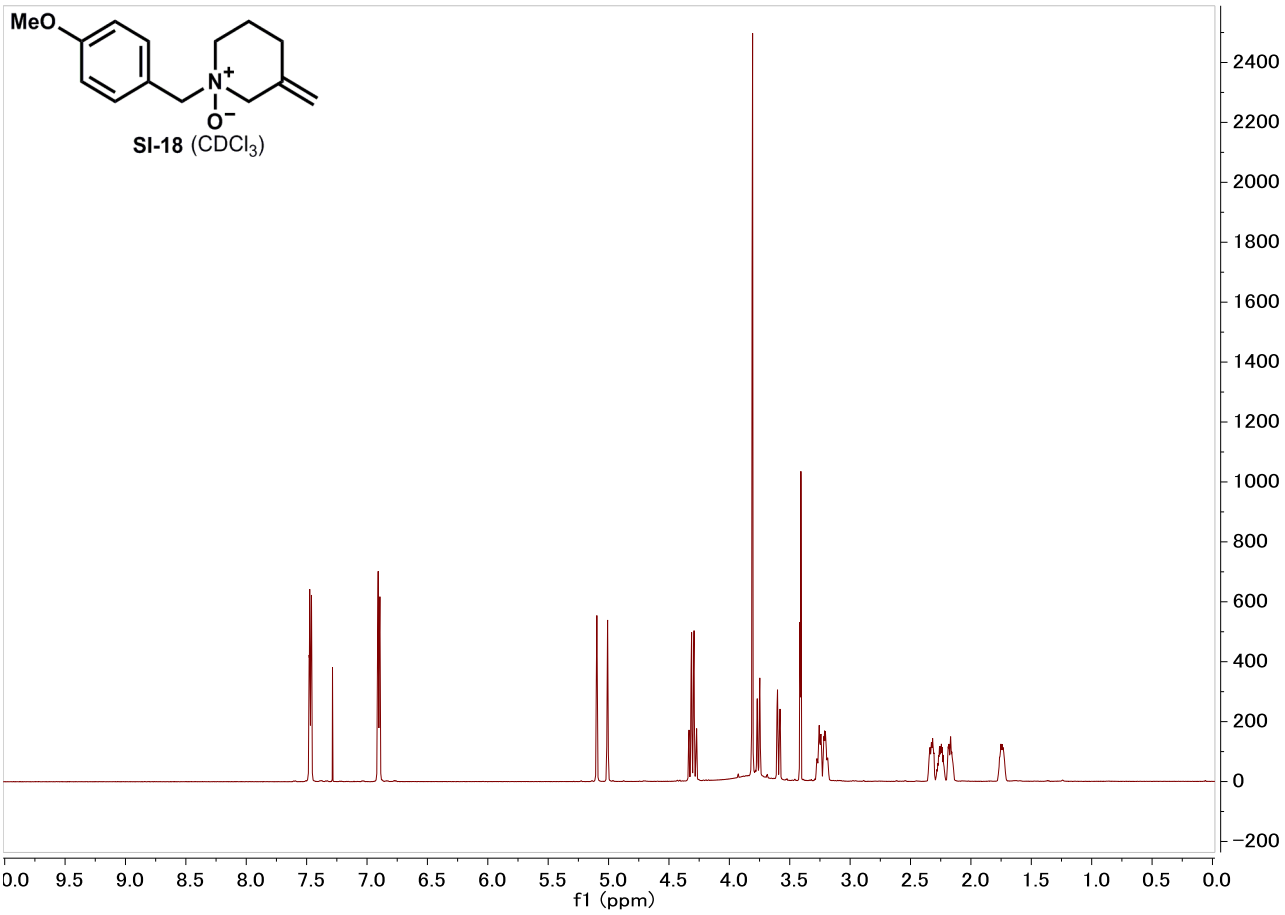

Ph
N
O
SI-14 (CDCl3)
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

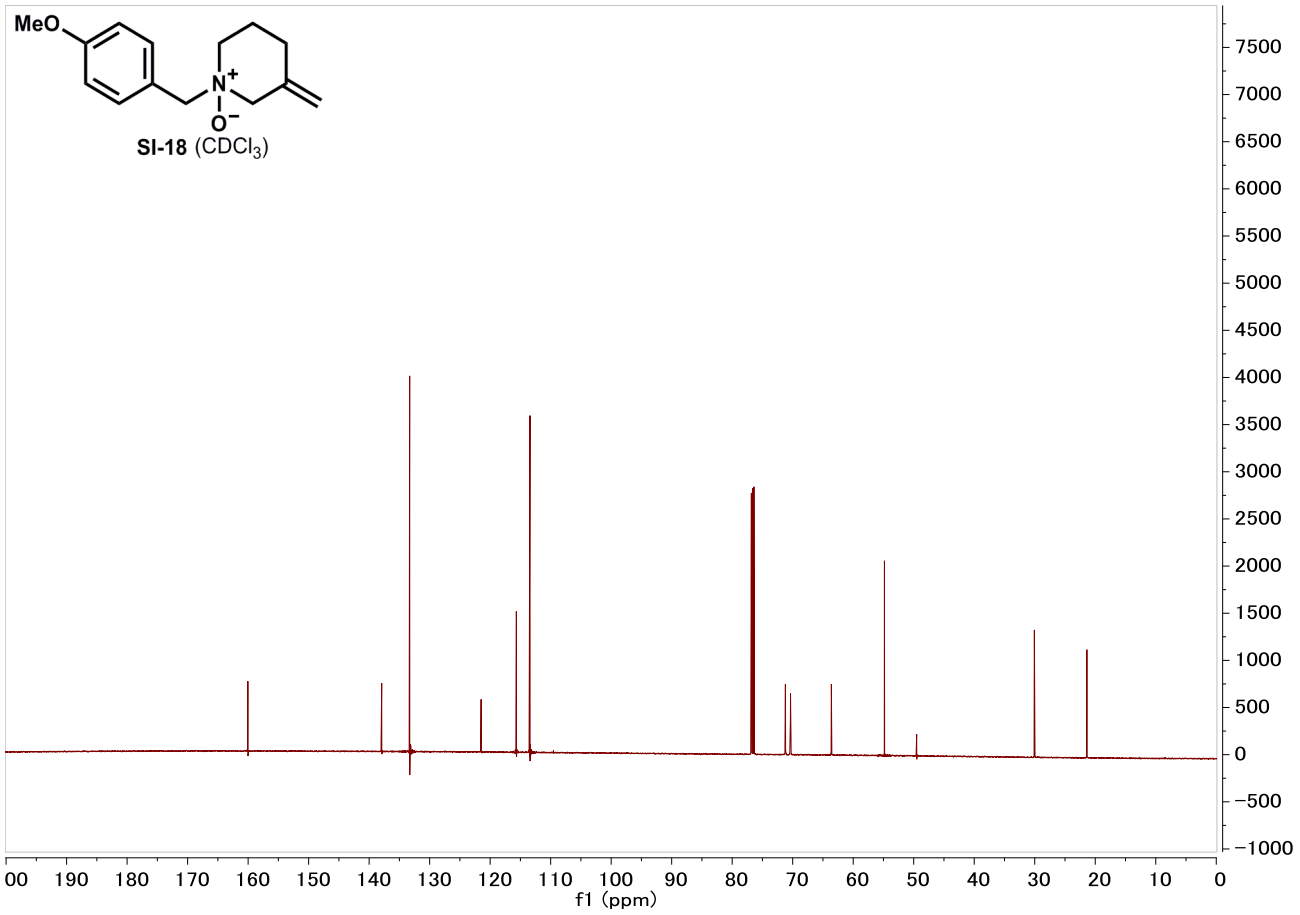

Ph
N
SI-15 (CDCl3)
1000
900
800
700
600
500
400
300
200
100
0
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

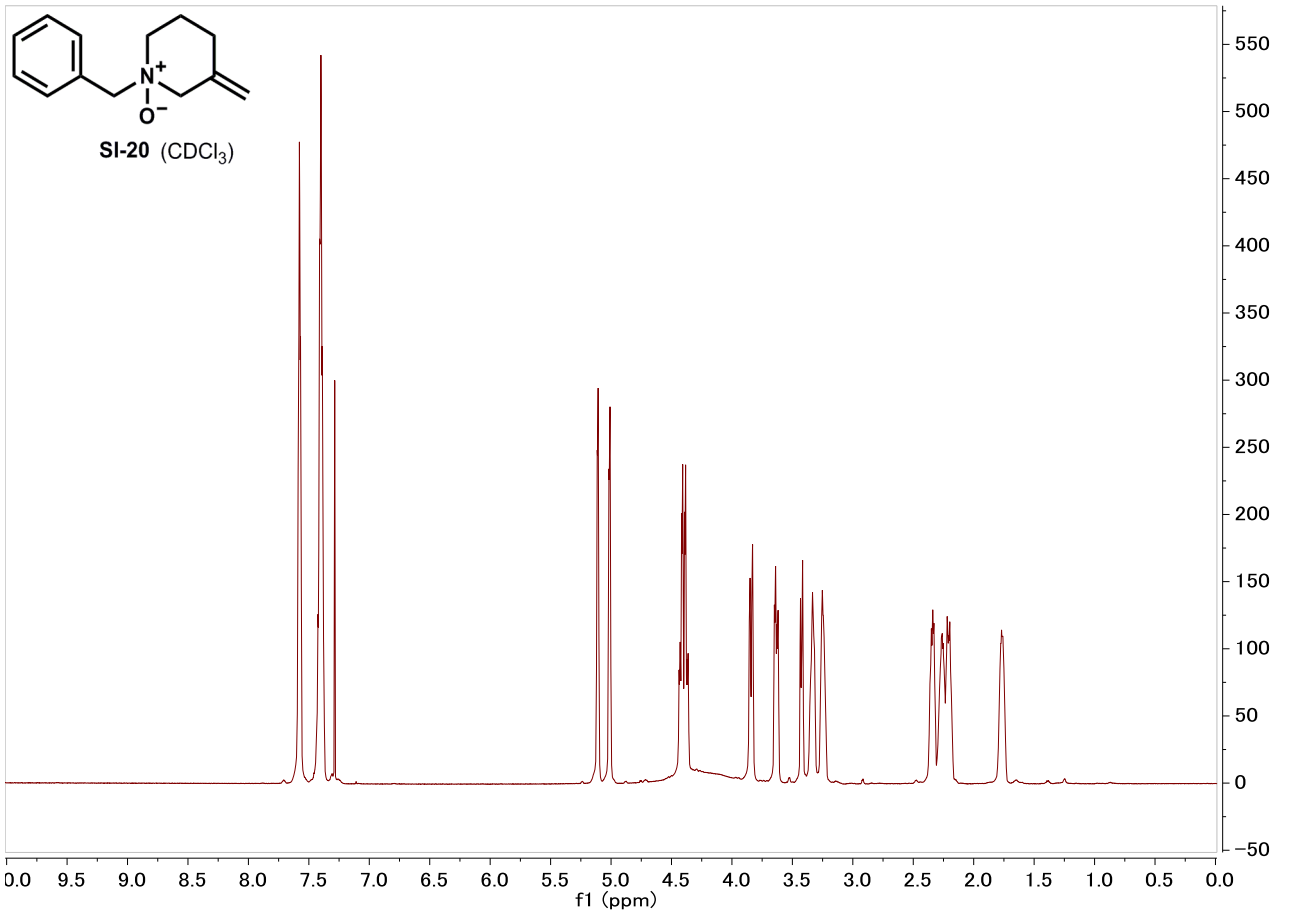

Ph
N
SI-15 (CDCl3)
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

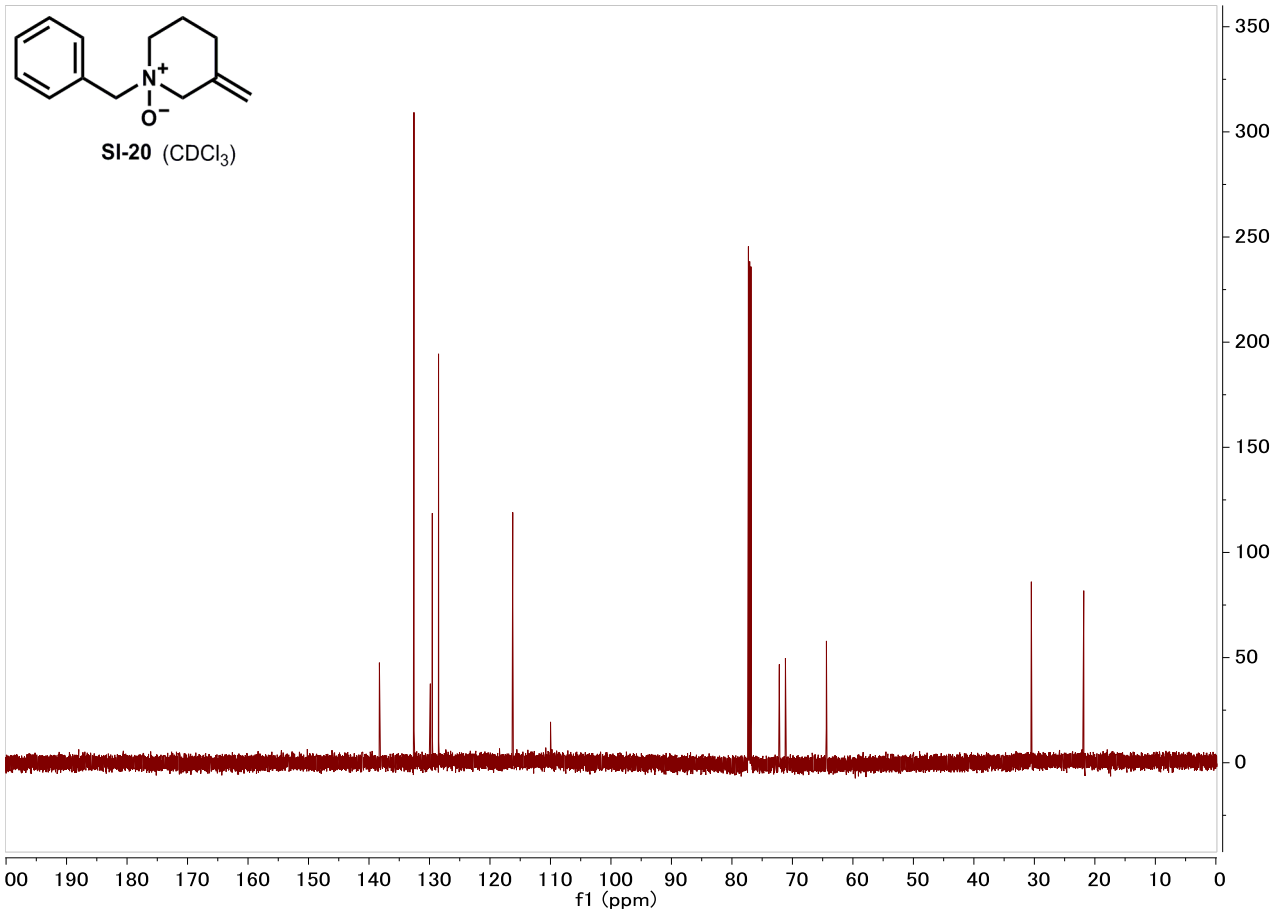

Ph
N+
O−
SI-16 (CDCl3)
1000
900
800
700
600
500
400
300
200
100
0
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

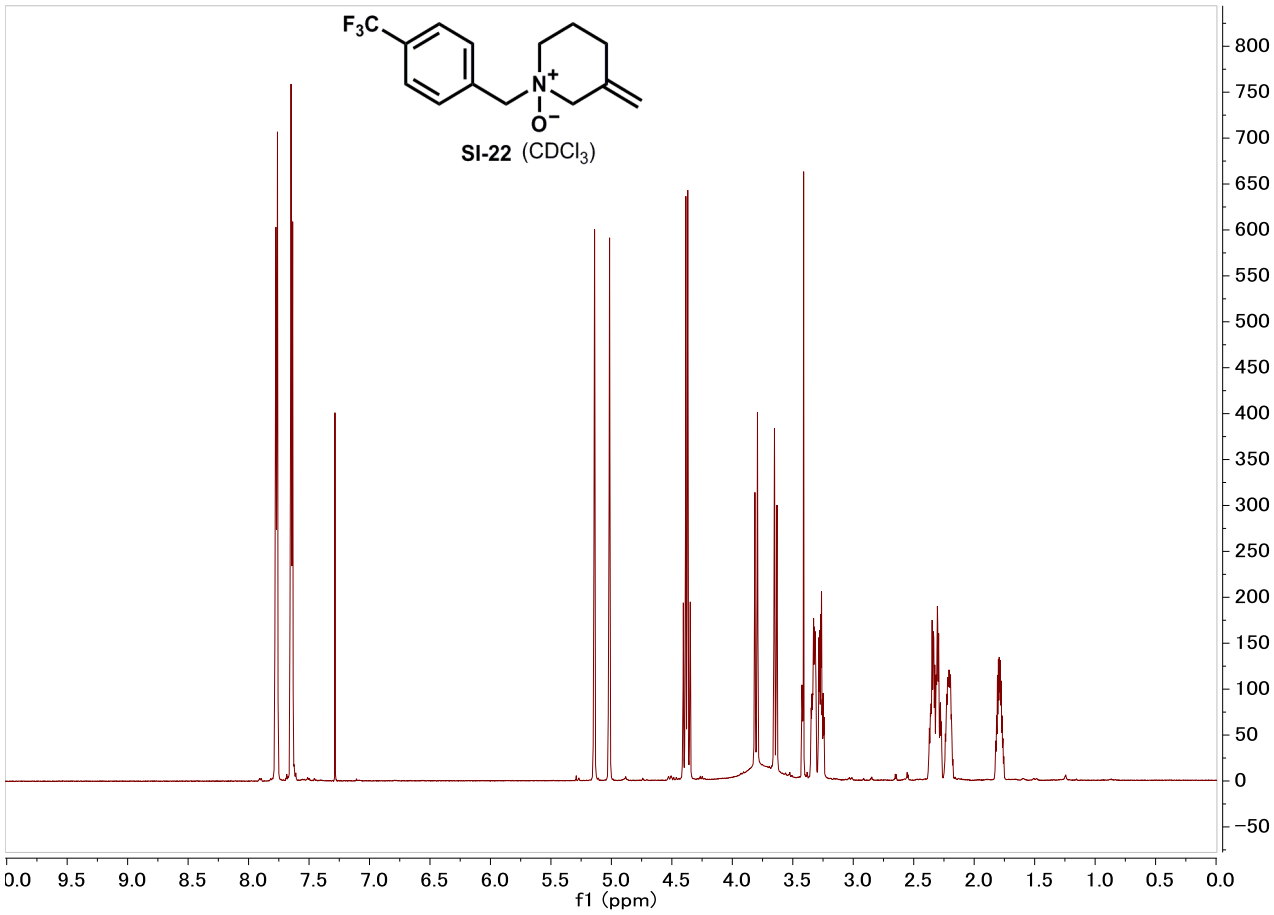

Ph
N+
O−
SI-16 (CDCl3)
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

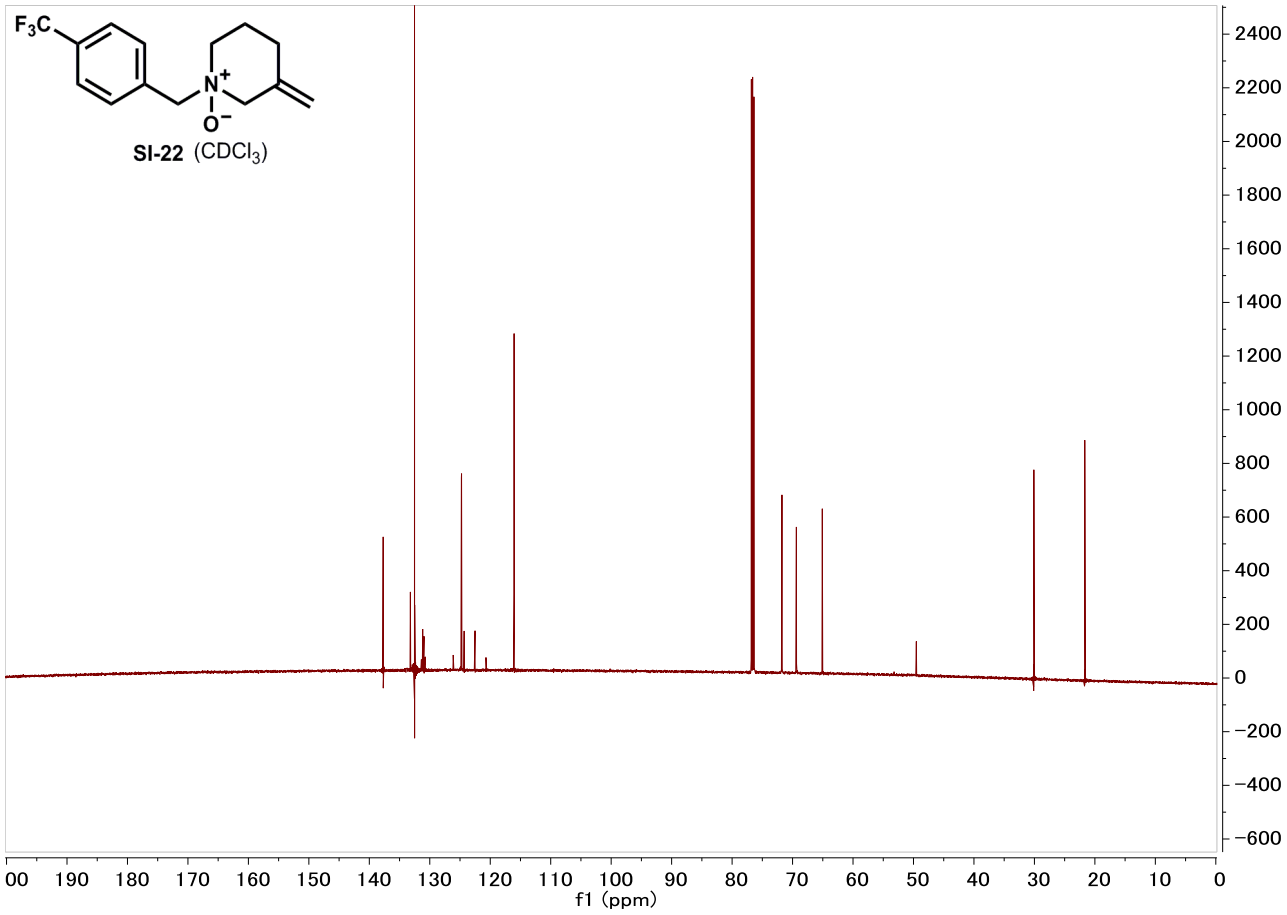

MeO
N+
O−
SI-18 (CDCl3)
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

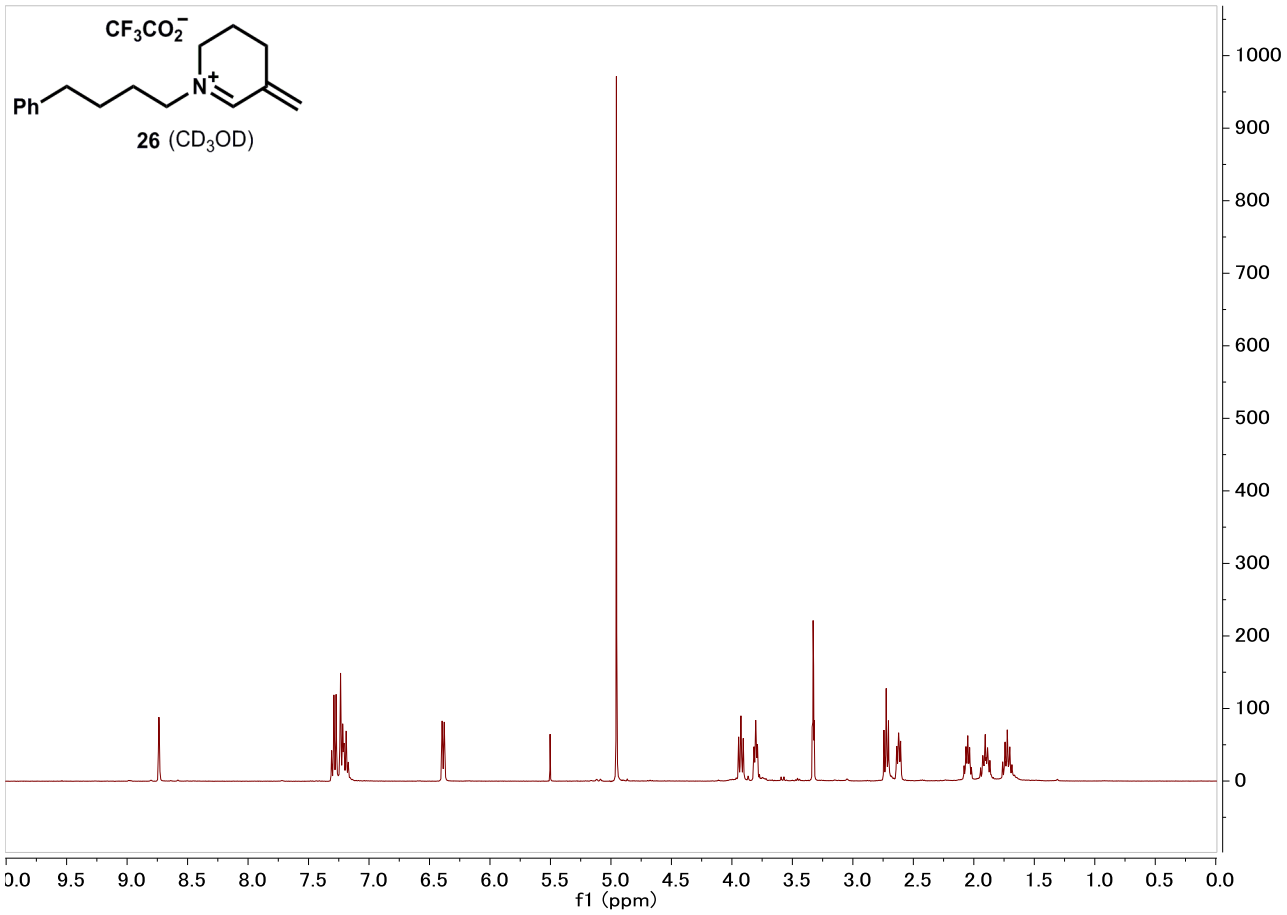

MeO
N+
O−
SI-18 (CDCl3)
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
−1000
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

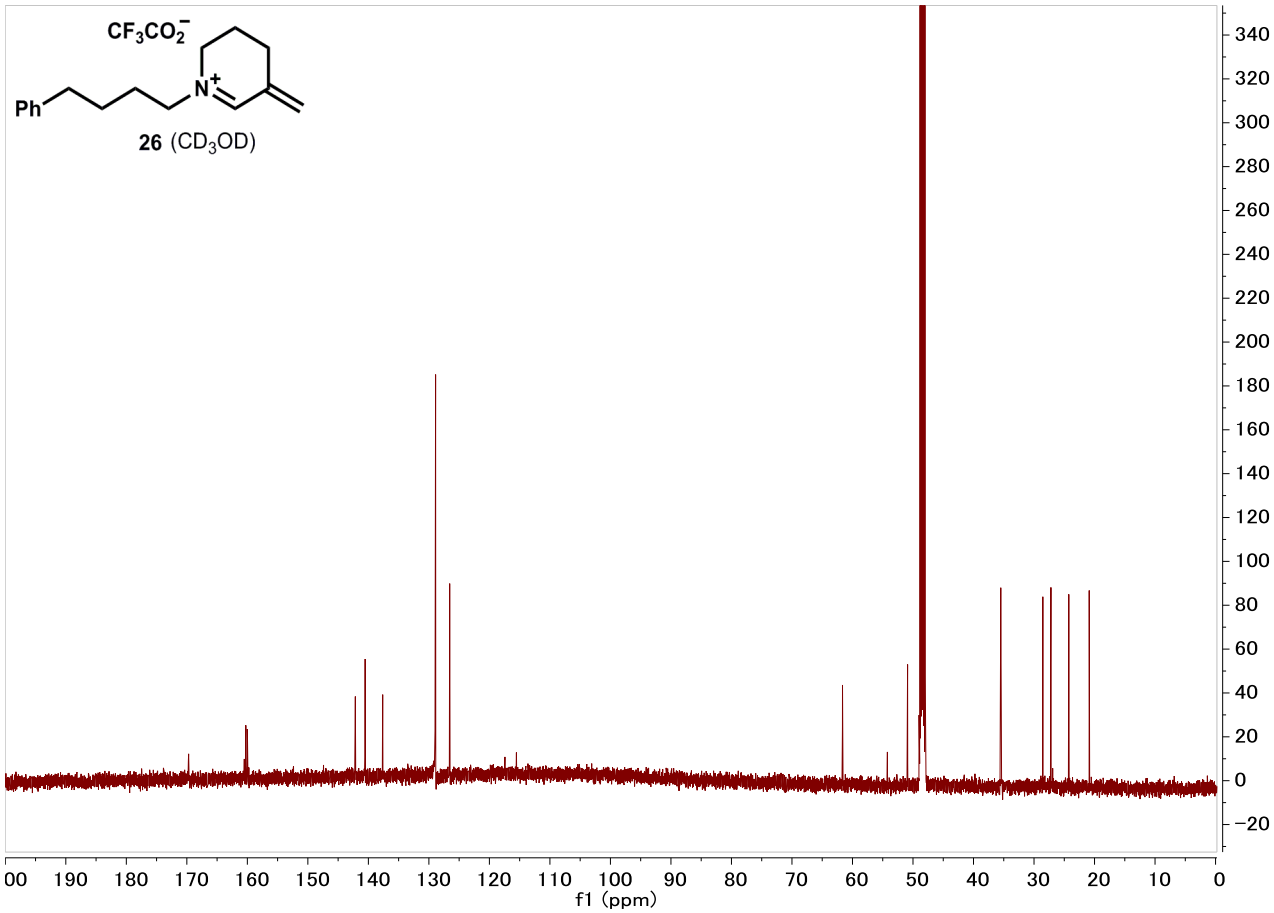

N+
O−
SI-20 (CDCl3)
550
500
450
400
350
300
250
200
150
100
50
0
−50
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

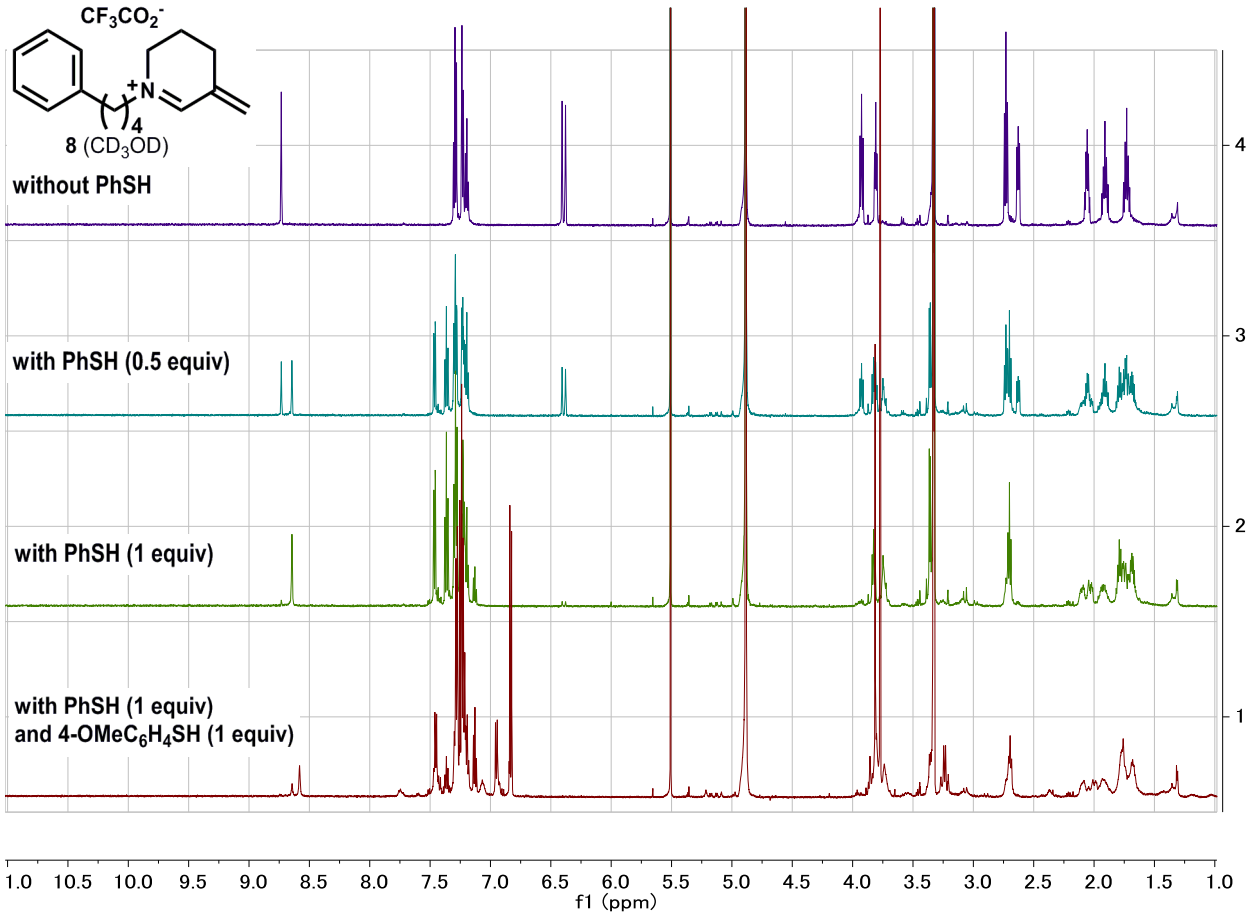

SI-20 (CDCl3)
f1 (ppm)

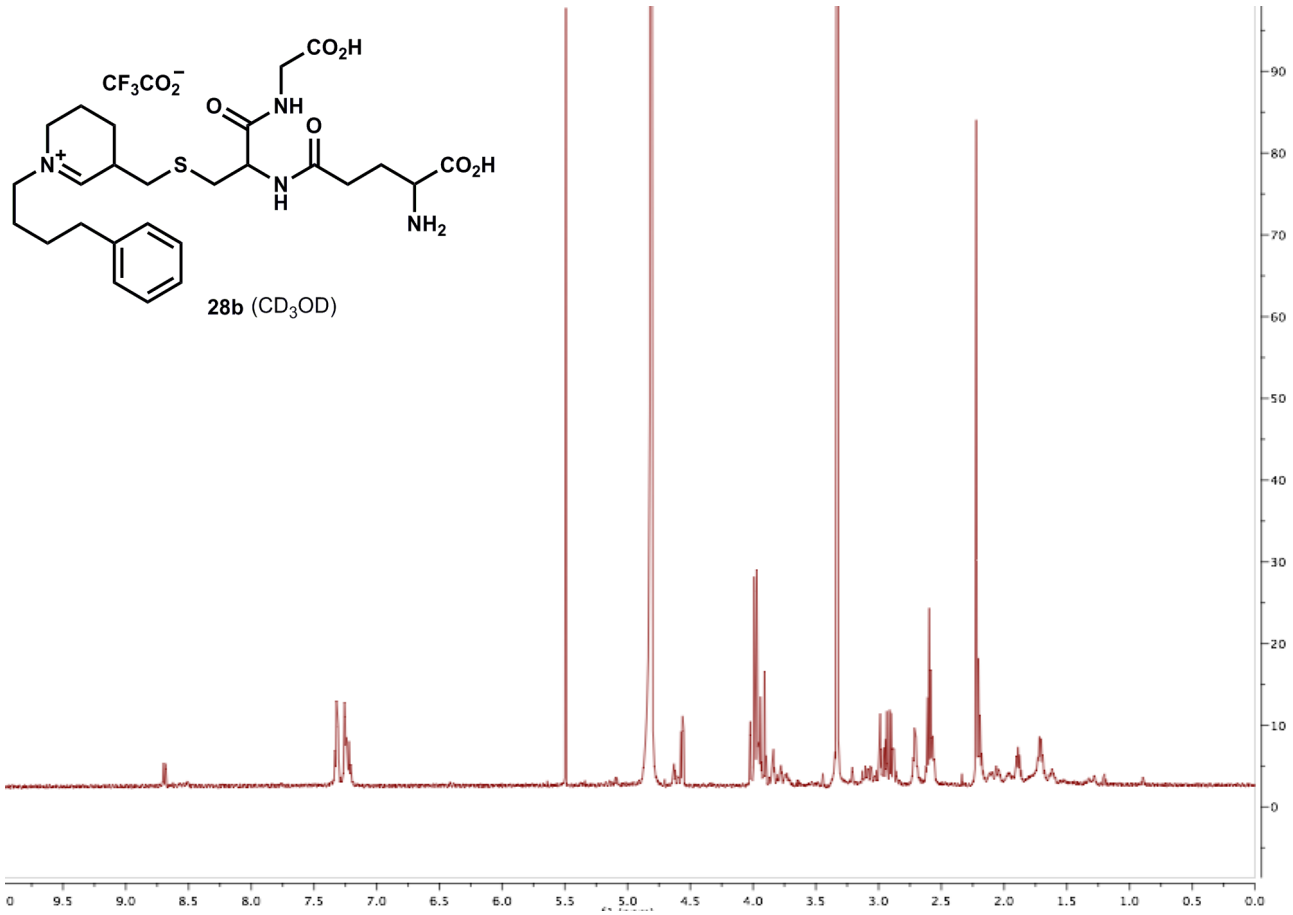

F3C
SI-22 (CDCl3)
f1 (ppm)


F3C
N+
O−
SI-22 (CDCl3)
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
−400
−600
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

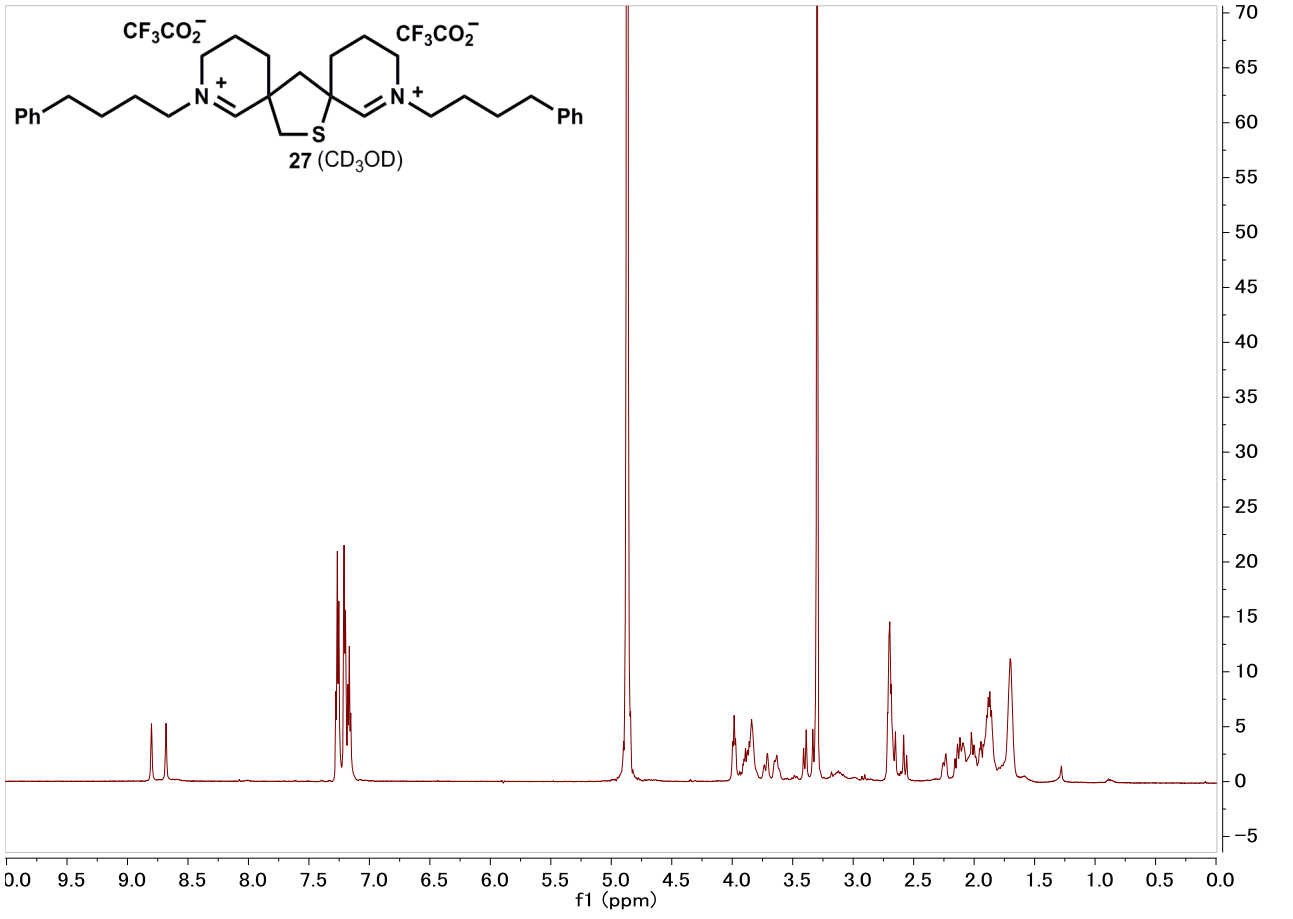

CF3CO2−
N+
Ph
26 (CD3OD)
1000
900
800
700
600
500
400
300
200
100
0
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


CF3CO2−
Ph
N+
26 (CD3OD)
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
−20
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CF3CO2-
N+
4
8 (CD3OD)
without PhSH
with PhSH (0.5 equiv)
with PhSH (1 equiv)
with PhSH (1 equiv)
and 4-OMeC6H4SH (1 equiv)
4
3
2
1
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

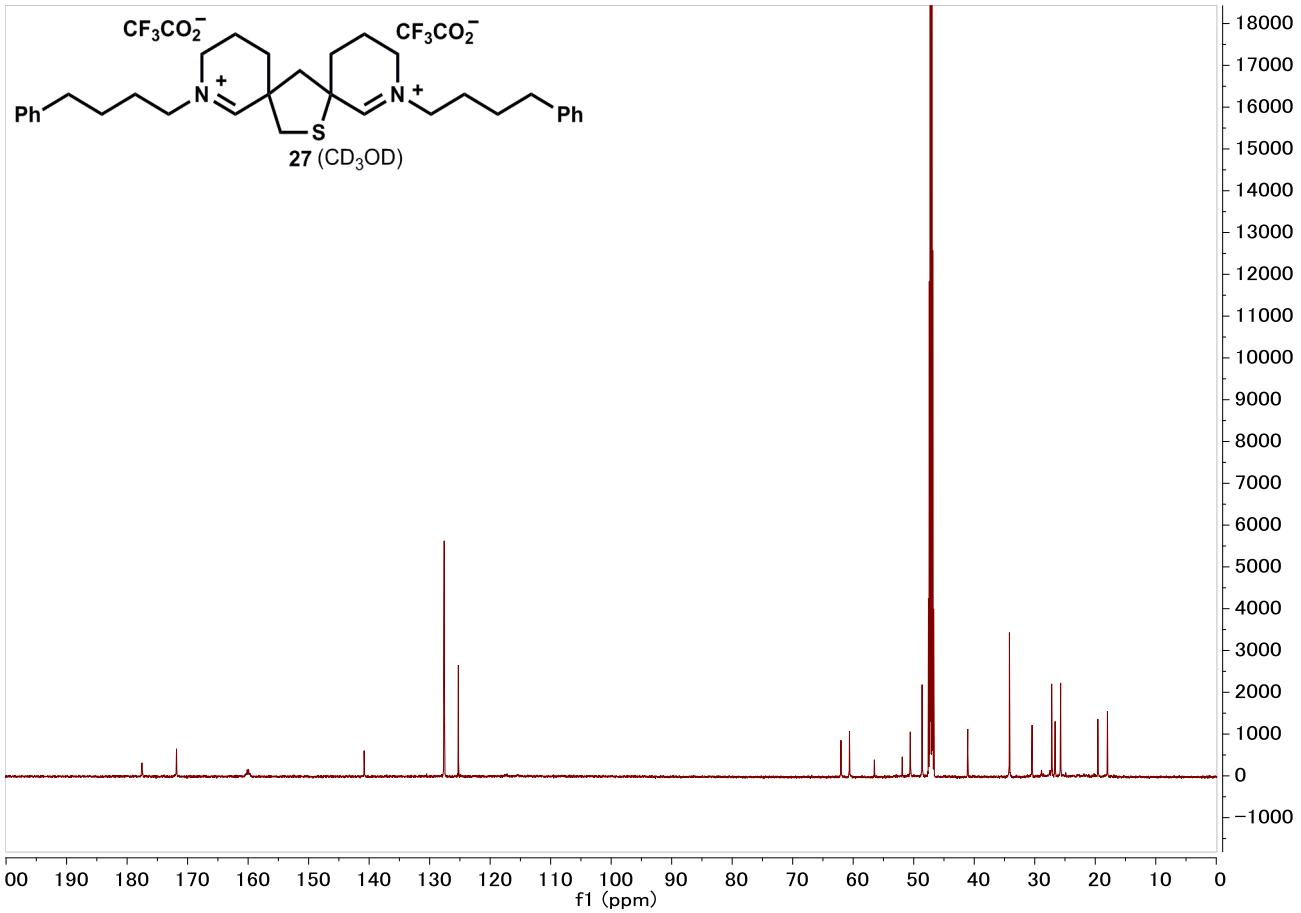


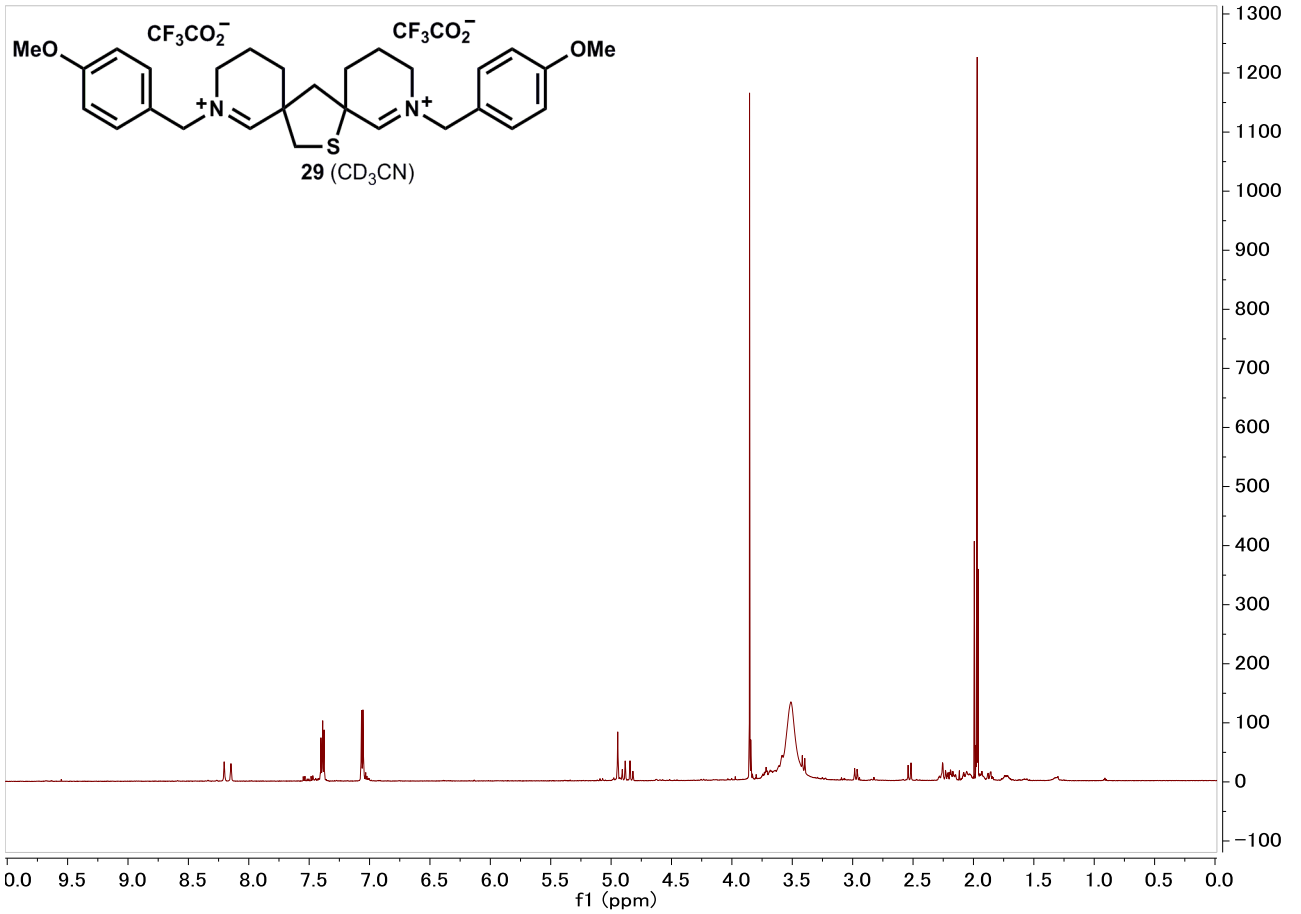
28b (CD_3OD)

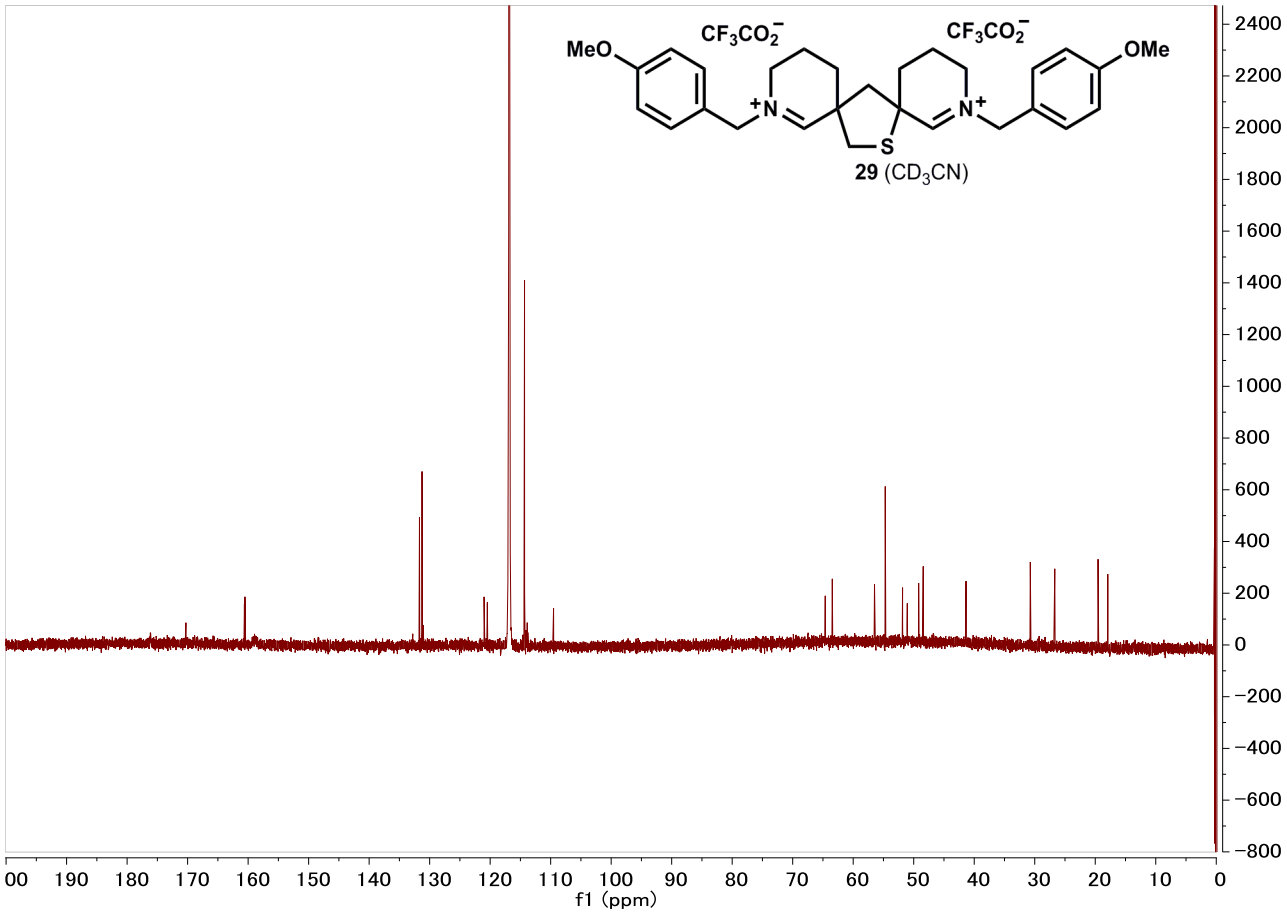


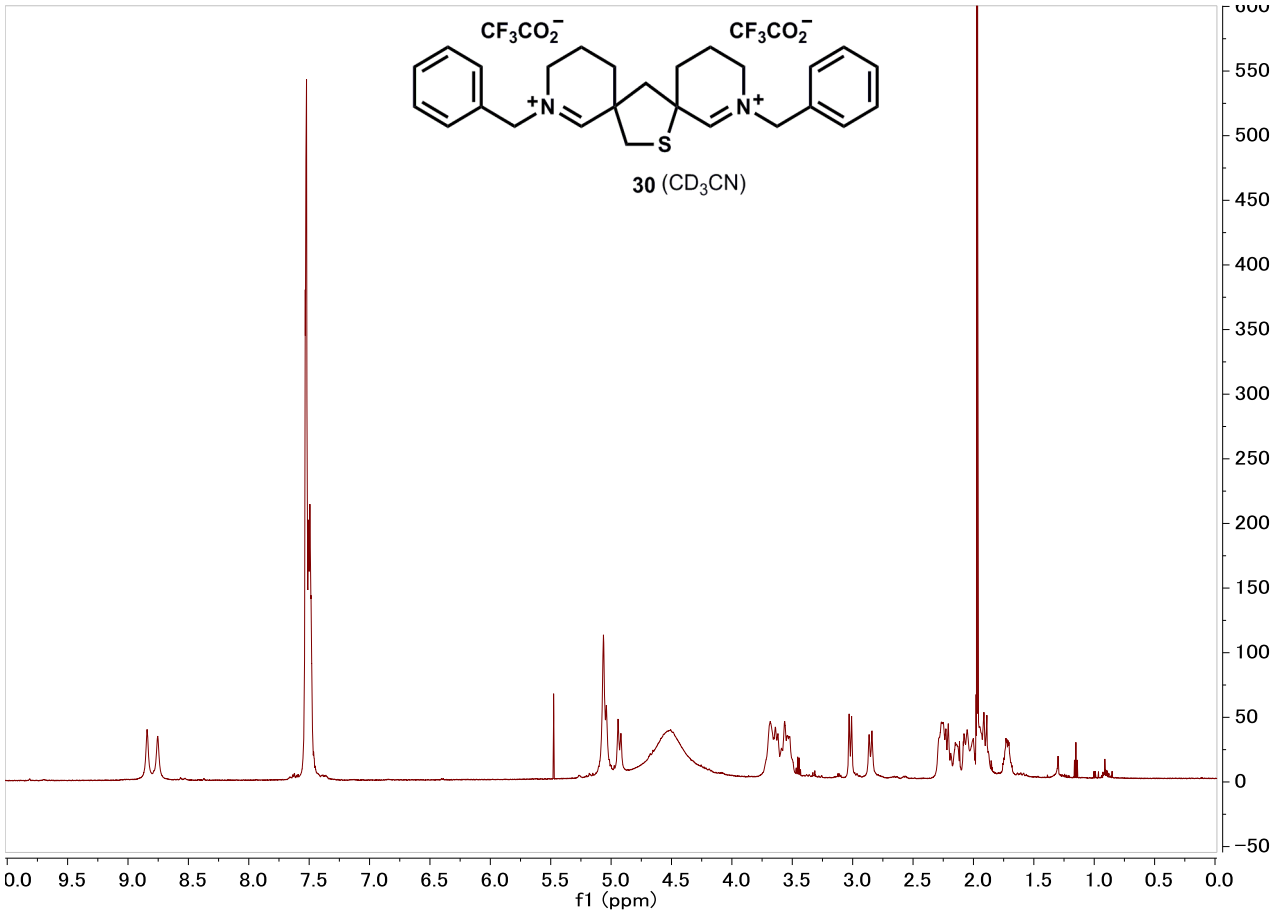
27 (CD_3OD)

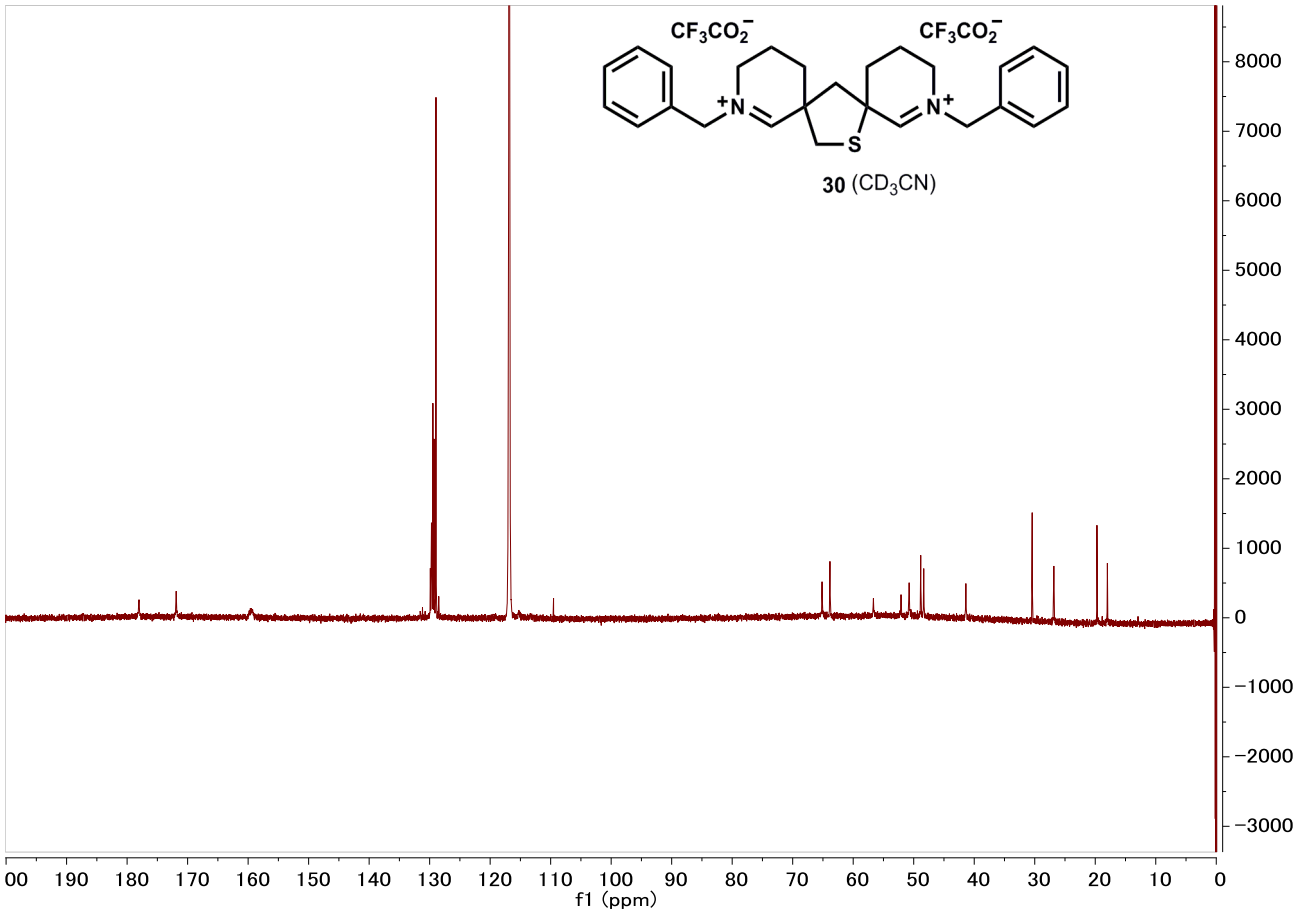
f1 (ppm)

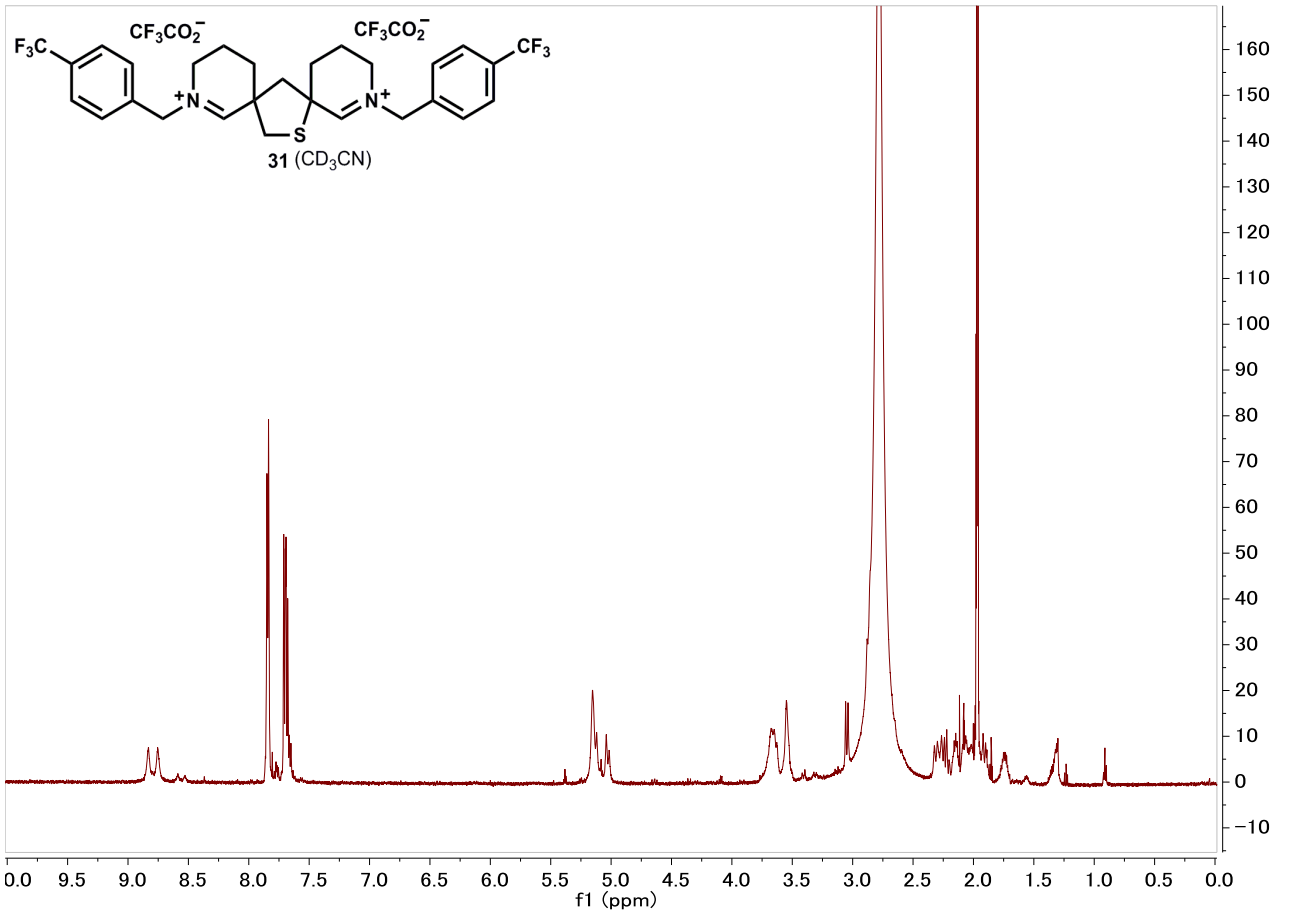

CF3CO2−
CF3CO2−
Ph
Ph
N+
N+
S
27 (CD3OD)
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

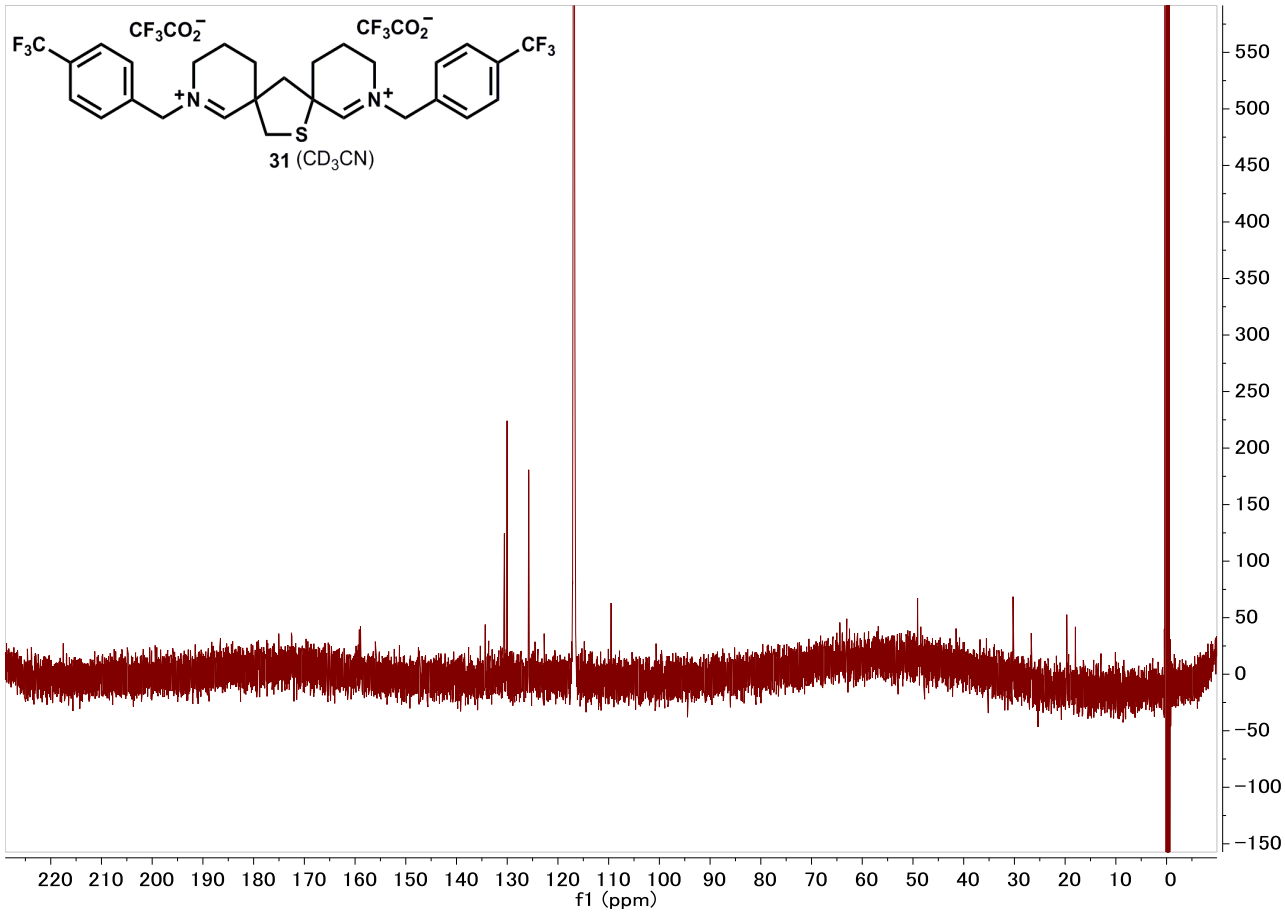

CF3CO2−
CF3CO2−
MeO
OMe
+N
N+
S
29 (CD3CN)
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

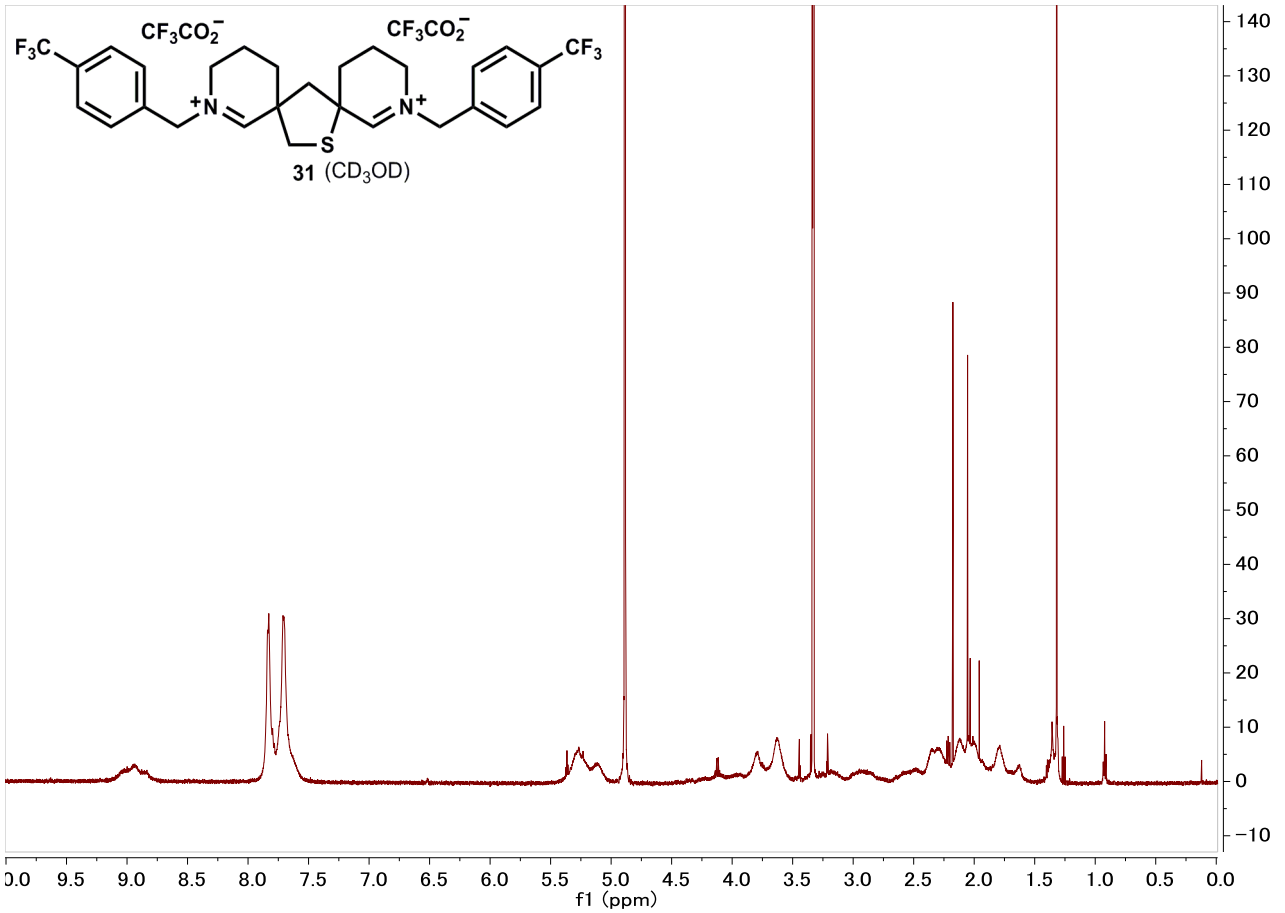

MeO
CF3CO2−
CF3CO2−
OMe
+N
N+
S
29 (CD3CN)
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
−400
−600
−800
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

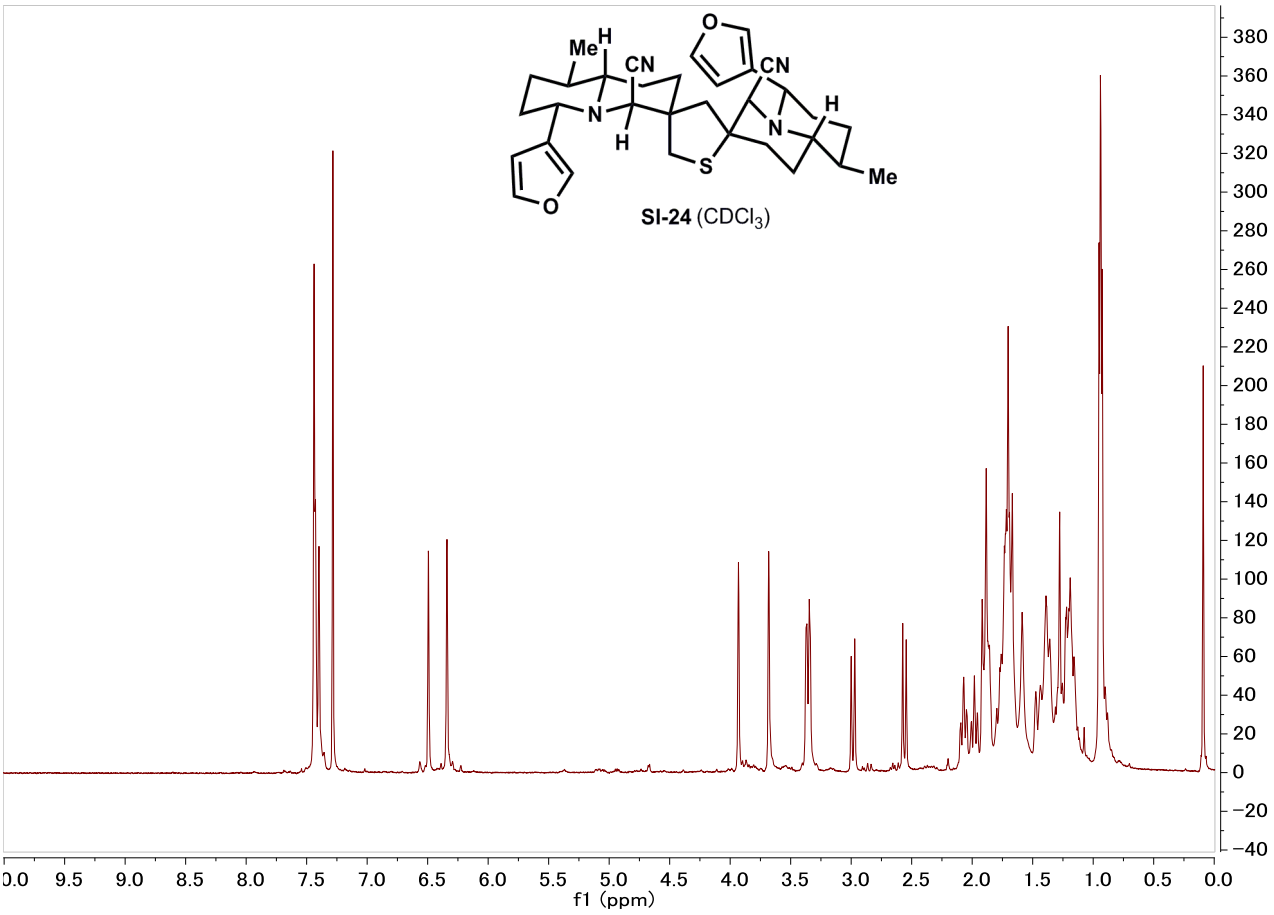

CF3CO2−
CF3CO2−
+N
N+
S
30 (CD3CN)
550
500
450
400
350
300
250
200
150
100
50
0
−50
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

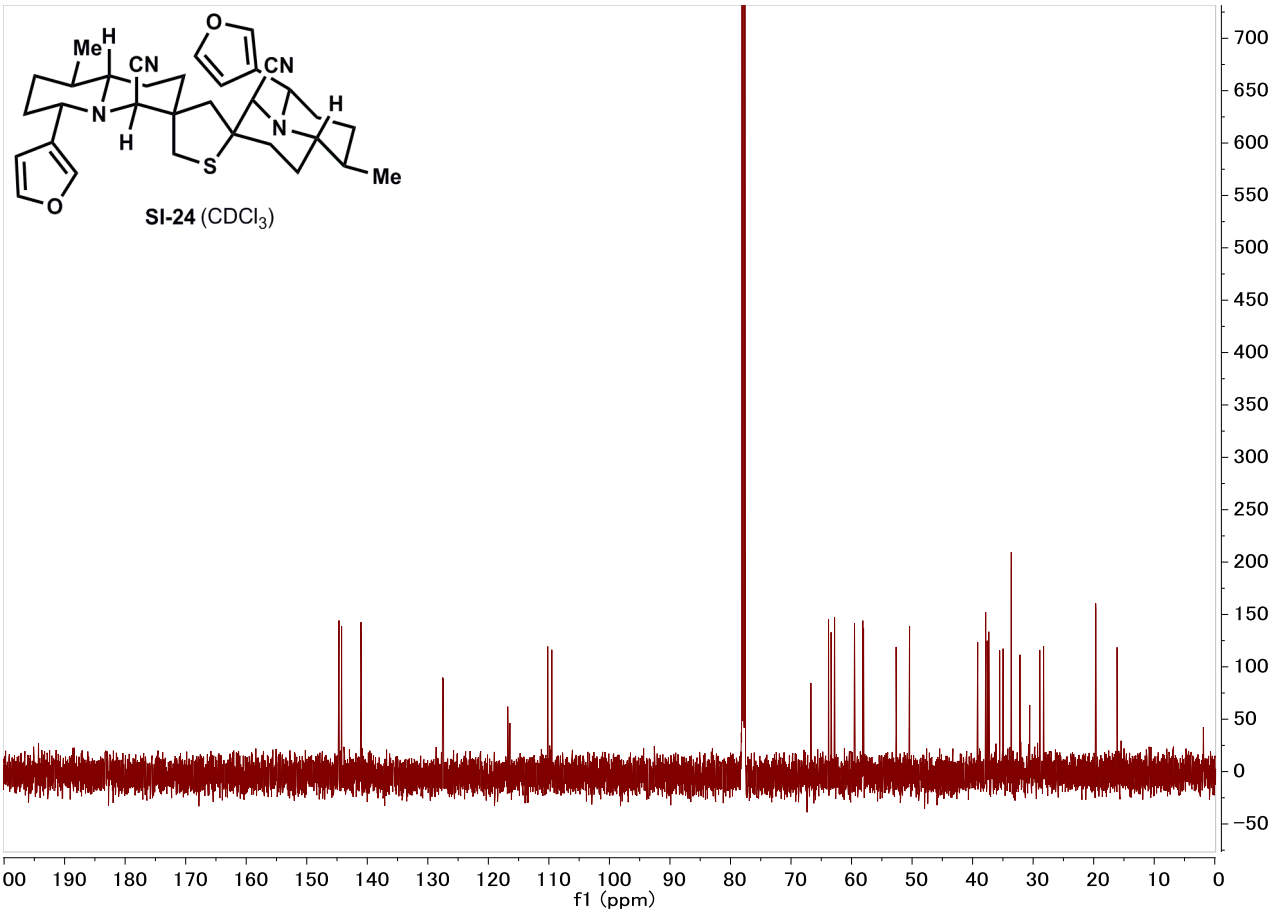

CF3CO2−
CF3CO2−
+N
N+
S
30 (CD3CN)
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
−2000
−3000
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

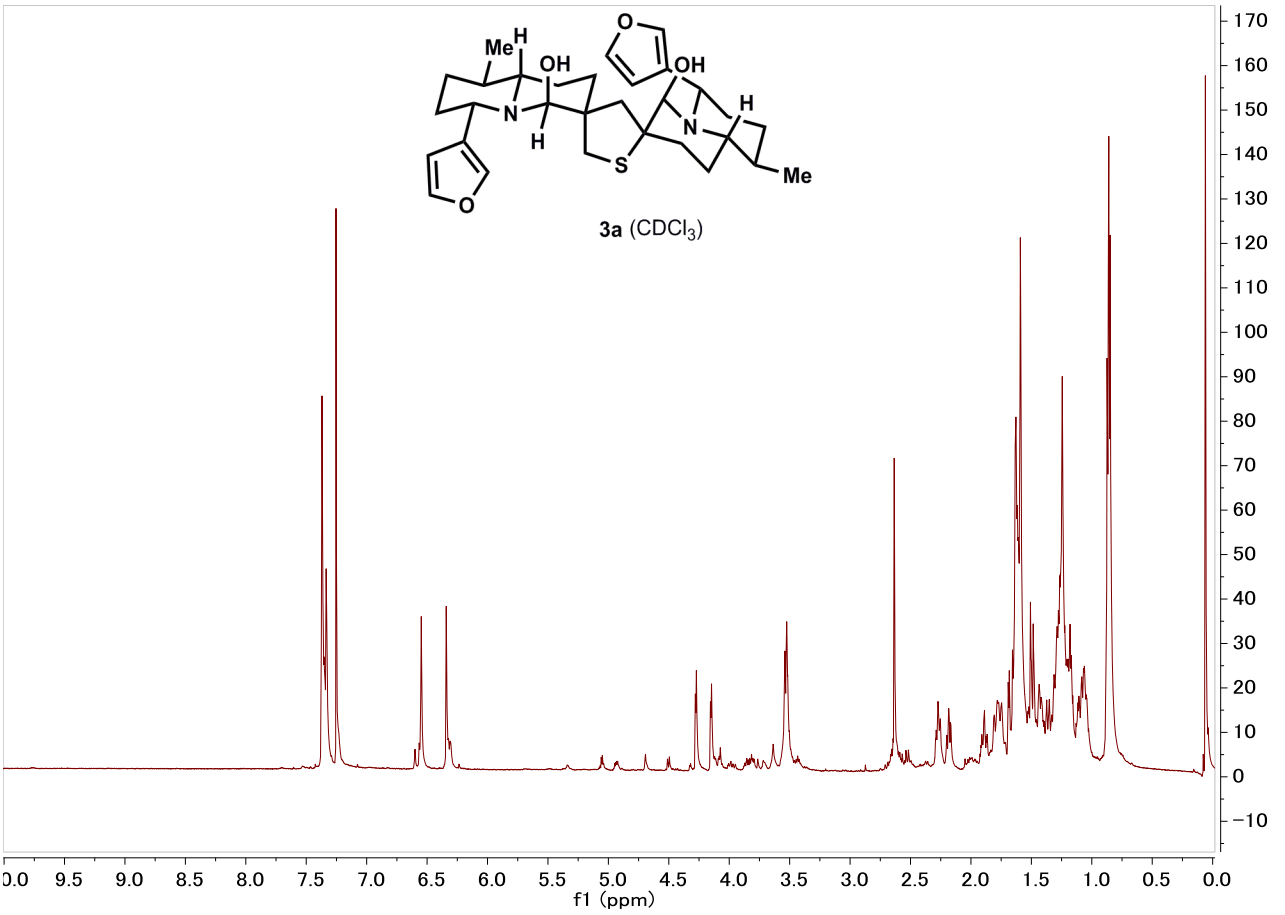

F3C
CF3CO2−
CF3CO2−
CF3
+N
N+
S
31 (CD3CN)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

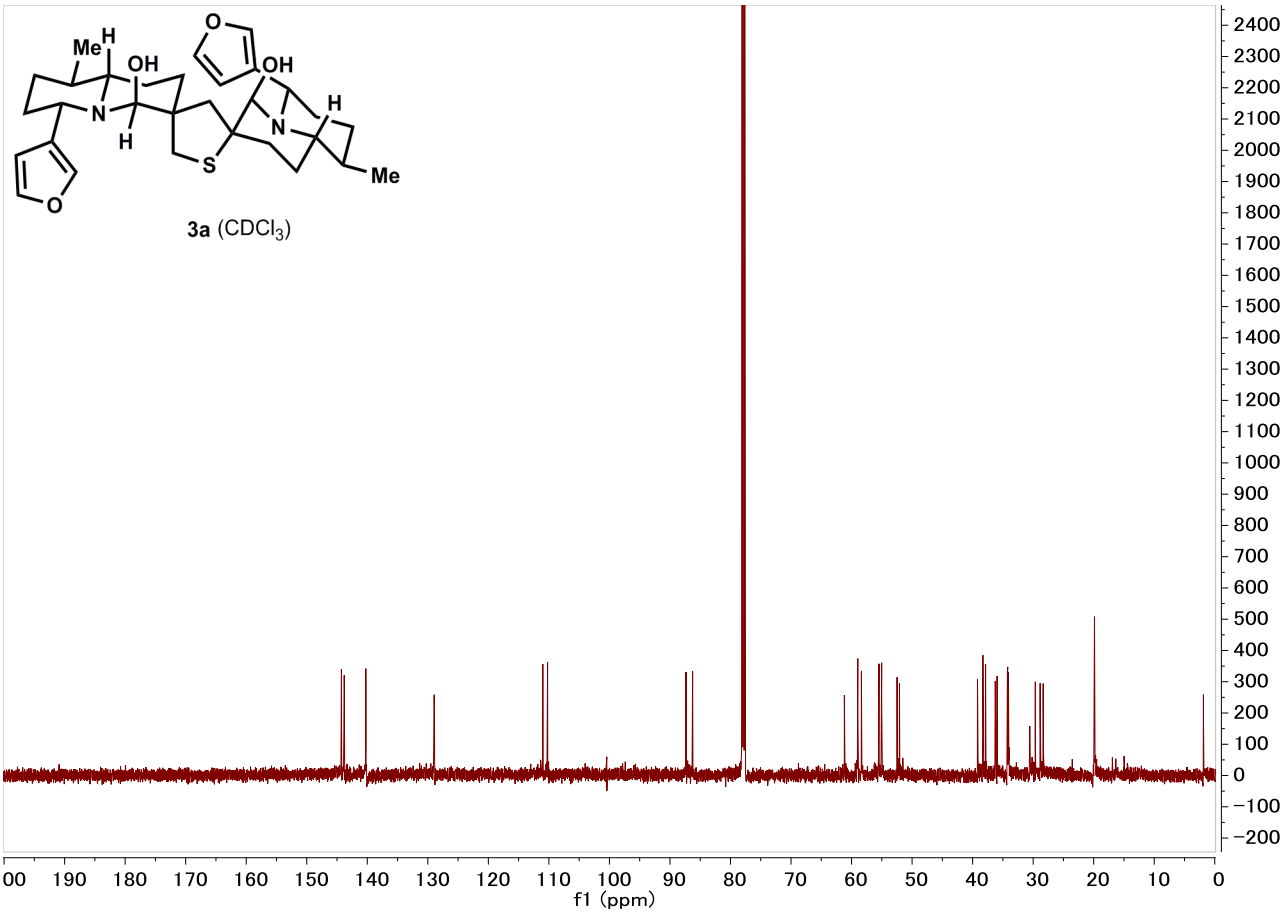

F3C
CF3CO2−
CF3CO2−
CF3
+N
N+
S
31 (CD3CN)
550
500
450
400
350
300
250
200
150
100
50
0
−50
−100
−150
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

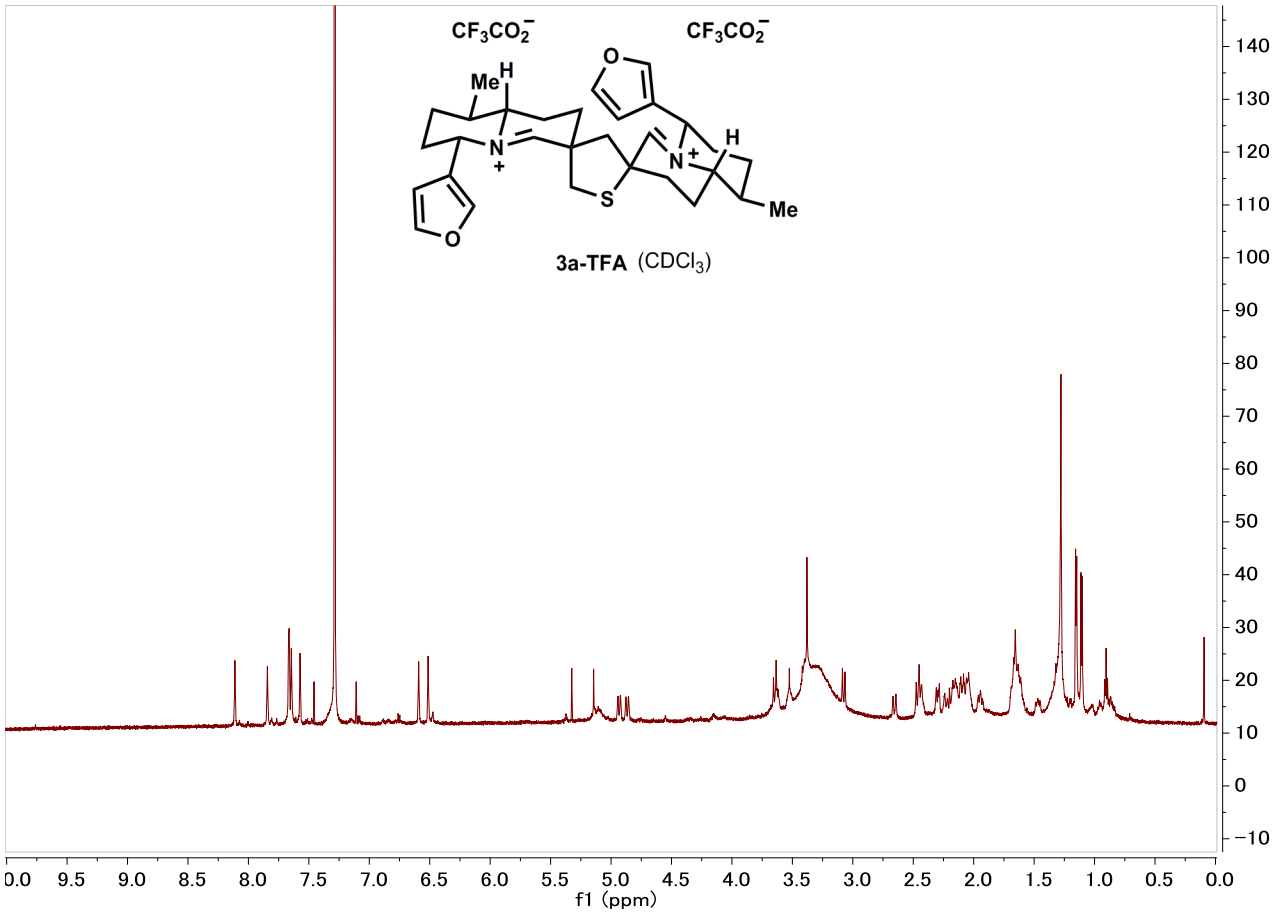

F3C
CF3CO2−
CF3CO2−
CF3
+N
N+
S
31 (CD3OD)
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


Me
H
CN
O
CN
N
H
N
H
S
Me
O
SI-24 (CDCl3)
f1 (ppm)


Me
H
CN
O
CN
N
H
N
H
S
Me
O
SI-24 (CDCl3)
f1 (ppm)


Me
H
OH
O
OH
N
H
S
N
H
Me
O
3a (CDCl3)
f1 (ppm)


Me
H
OH
O
OH
N
H
S
N
H
Me
O
3a (CDCl3)
f1 (ppm)


CF3CO2−
CF3CO2−
Me
H
N+
O
S
N+
H
Me
O
3a-TFA (CDCl3)
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)